Medicinal Plants and the Heart

Barbara L. Bean
MD., PhD., FACC
Figure 7-1 Relief of dropsy (P Barbette, 1672).
The man credited with the introduction of digitalis into the practice of medicine was William Withering. Withering was born in Wellington, Shropshire, England in 1741. He followed in the medical footsteps of his father who was an apothecary-surgeon. Withering received his MD degree in 1766.

As an individual, William Withering was an extremely giving person. He would personally see and treat two or three thousand poor patients a year limiting him to making about 1000 British pounds as compared to his contemporary doctors who made 5000 British pounds per year.

Withering published about 19 articles during his lifetime. After fighting a long battle with tuberculosis, William Withering, the father of digitalis medicine, died on October 6 1799, at the age of 58.

Digitalis purpurea in Witherings 18th century was a blessing for people with dropsy. At the same time, foxglove concoctions began to appear in an attempt to cure, albeit unsuccessfully, illnesses such as asthma, epilepsy, hydrocephalus, insanity and others. The 18th century brought foxglove into medical light, but it would take several hundred years before its true healing powers could be harnessed completely.
LEADING CAUSES OF DEATH FOR ALL MALES AND FEMALES

United States - 2002

Deaths in Thousands

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>455</td>
<td>61</td>
<td>53</td>
<td>37</td>
<td>256</td>
</tr>
<tr>
<td>B</td>
<td>281</td>
<td></td>
<td></td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>C</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>D</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>E</td>
<td>37</td>
<td></td>
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</tr>
</tbody>
</table>

A: Total CV Diseases  C: Accidents  E: Pneum/Influenza
B: Cancer  D: Obstr Pulm Dis  F: Diabetes Mellitus

National Center for Health & Statistics and AHA 2002
DEATHS FROM CARDIOVASCULAR CAUSES, WORLDWIDE, IN 1990 AND ESTIMATED FOR 2020

- Western countries
- Non-Western (developing) countries

 Millions of Deaths from Cardiovascular Causes

<table>
<thead>
<tr>
<th>Year</th>
<th>Western</th>
<th>Non-Western</th>
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<tbody>
<tr>
<td>1990</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>2020</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

KS Reddy. NEJM 2004; 350:2438
Traditional Risk Factors

1. Gender (male)
2. Age
3. Family History
4. Elevated LDLC
5. Smoking
6. Diabetes
7. Elevated Blood Pressure
8. Exercise and weight
9. Low HDLC
10. Uric Acid?
PREVALENCE OF MAJOR RISK FACTORS IN THE UNITED STATES

Number of Risk Factors

Age, BP, DM, Smoking, LDL-C, HDL-C, Obesity, Inactivity, FH Premature CHD

KJ Greenlund et al., Arch Intern Med 2004:164:181
## RISK FACTORS FOR WHICH INTERVENTION IS PROVEN TO LOWER RISK

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on CHD</th>
<th>Effect on DP</th>
<th>Effect on Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation</td>
<td>↓ 10%</td>
<td>DP ↓ 6 mmHg</td>
<td></td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td>50% ↓ CHD</td>
<td></td>
<td></td>
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<tr>
<td>Cholesterol</td>
<td></td>
<td>30% ↓ CHD</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>16% ↓ CHD, 42% ↓ Stroke</td>
</tr>
</tbody>
</table>

CH Hennekens, Circ 1998; 97:1095
How Does A Heart Attack Happen?

1. Damage to endothelium.
2. Infiltration of macrophage cells.
3. Formation of foam cells.
4. Organized plaque.
5. Rupture of plaque.
6. Formation of thrombus and vessel occlusion.
The Progression of Atherosclerosis

Healthy artery
Early stages of atherosclerosis
Inflammatory process
Early atherosclerotic lesions
Vulnerable plaque
Stable plaque

Intravascular ultrasound (IVUS) images compiled by the Cleveland Clinic.
Comparison of Vulnerable and Stable Plaques

"Vulnerable" Plaque
- Lumen
- Lipid Core
- Fibrous cap
- Media

"Stable" Plaque
- Lumen
- Lipid Core

T-Lymphocyte
- Macrophage
- Foam cell (Tissue Factor*)
- "Activated" intimal SMC (HLS-DR*)
- Normal Medial SMC
CT- Calcified and Obstructive lesion LAD

CTA-MIP

Angiography
Relationship Between Cholesterol and CHD Risk

MRFIT (Multiple Risk Factor Intervention Trial)

CHD risk based on total cholesterol (TC) level

- Each 1% decrease in total cholesterol level is associated with a 2% reduction in CHD risk
  — Framingham Heart Study

Log-Linear Relationship Between LDL-C Levels and Relative Risk for CHD

Relative Risk for Coronary Heart Disease (Log Scale)

LDL-Cholesterol (mg/dL)

Cholesterol

1. LDL or “Bad cholesterol”

2. HDL or “Good cholesterol”

3. Triglycerides (VLDL) derived from excess sugar.
Low Density Lipoprotein

The major carrier of cholesterol to the periphery. Essential for the integrity of nerve tissue, steroid synthesis and cell membranes.

Subclasses, e.g. Pattern B LDL, or “small dense LDL” is associated with a three fold risk of CAD. Composition varies with triglyceride levels, age and estrogen. Oxidized LDL; attaches to monocytes which adhere to the arterial wall.
High Density Lipoprotein (good cholesterol)

• Secreted by the liver and involved in reverse transport of LDL from cells into the liver for secretion into the bile or reconstitution into cell membranes or VLDL

• Protective mechanism is unclear, but high levels may reflect rapid clearance of triglyceride rich atherogenic particles. May also be associated with enhancement of endothelial repair.

• Apolipoprotein A1 deficiency is associated with markedly decreased HDL levels and an increase in the incidence of atherosclerosis.
HYPERTRIGLYCERIDEMIA

Direct association between triglyceride levels and cardiac risk.

e.g. Helsinki Heart study determined a 3.8% greater risk of cardiac events when the triglyceride level was greater than 200mg/dl.
## Recent Landmark Coronary Prevention Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Duration (Years)</th>
<th>Main Findings</th>
</tr>
</thead>
</table>
| 4S†        | Simvastatin | 4,444 | 5                | ↓ 30% total mortality  
            |           |       |                  | ↓ 34% coronary events*  |
| WOS‡       | Pravastatin | 6,595 | 5                | ↓ 31% coronary events  
            |           |       |                  | ↓ 22% total mortality  |
| CARE+++    | Pravastatin | 4,159 | 5                | ↓ 24% coronary events  
            |           |       |                  | ↓ 31% stroke  |
| AFCAPS/TexCAPS+++ | Lovastatin | 6,605 | 5                | ↓ 37% coronary events/unstable angina  
            |           |       |                  | Low HDL population  |
| LIPID†     | Pravastatin | 9,014 | 6                | ↓ 22% total mortality  
            |           |       |                  | ↓ 24% death from CHD  |


*Nonfatal MI/CHD death  † Secondary prevention  ‡ Primary prevention  ** Normal cholesterol levels
Changes from (Post-ACS) Baseline in Median LDL-C

Note: Changes in LDL-C may differ from prior trials:
- 25% of patients on statins prior to ACS event
- ACS response lowers LDL-C from true baseline

Median LDL-C (Q1, Q3)
- Pravastatin 40mg: 95 (79, 113)
- Atorvastatin 80mg: 62 (50, 79)

Graph showing the percentage decrease in LDL-C for Pravastatin and Atorvastatin at different time points.
All-Cause Death or Major CV Events in All Randomized Subjects

- Pravastatin 40mg (26.3%)
- Atorvastatin 80mg (22.4%)

16% RR (P = 0.005)

% with Event vs. Months of Follow-up
REVERSAL Trial

Percent Reduction in CRP

\[ p < 0.001 \]

-36.4% for Atorvastatin
-5.2% for Pravastatin

AHA 2003, Orlando, FL
Complimentary or Integrative medicines

Where do they fit in?
Most Common CAM Therapies

- Chiropractic
- Massage
- Herbal Remedies
- Relaxation Techniques

Used by >10% of the population
Reasons for Non-Disclosure of CAM Therapy
(n=726 National Survey)

- Not important for MD to Know  61%
- Doctor never asked  60%
- None of the MD’s business  31%
- Doctor would not understand  20%
- Doctor would disapprove  14%
- Doctor would discourage  13%

Eisenberg D, Ann Intern Med 2001
SUPPLEMENTS for CV DISEASE

- Antioxidants
- Plant Sterols
- Soluble Fiber
- Omega-3 fatty acids
- Soy
- B-Vitamins
- Minerals
- Herbs
Antioxidants

- Beta carotene and vitamin A
- Tocopherols (vitamin E)
- Ascorbic Acid (vitamin C)
Antioxidant Vitamins and CV Disease

Observational Studies

Nurses Health Study

121,700 U.S. females 30-55 yrs

Dietary History

34% risk reduction in CV disease with Vitamin E supplements

Advances CV Medicine

1995
Vitamin E Primary Prevention

- ATBC
- Health Professional Follow up Study (37%RR)
- Nurses Health Study
- Iowa Women’s Study
- Primary Prevention Project: 4495 pts. 3.6 years F/U 300IU Vitamin E failed to demonstrate a reduced risk of CVD events
Vitamin E Hope Trial

- 2,545 women and 6,996 men > 54 y/o
- High risk of CV events because of known CV disease or DM and one other risk
- 2x2 multifactorial design 400 IU vitamin E or placebo and ramipril or placebo
- Followed 4.5 years

Vitamin E Hope Trial

- Primary outcome was composite of MI, CVA or Death from CVD
- Primary outcome events 16.2% Vitamin E and 15.5% placebo
- No difference in secondary outcomes or Mortality
Vitamin E Secondary Prevention

- CHAOS: Reduced risk of non-fatal MI by 75%
- HOPE: No benefit
- GISSI-P: No benefit
- VEAPS: No benefit
- SPACE: Decreased CV death and non-fatal MI
- Meta-analysis of 81,788 pts. No benefit in mortality.
Combination Vitamin Trials
HPS Collaborative Group
Lancet.360(9326):23-33,2002

- HPS: 20,000 subjects high risk CHD randomized to 40mg Simvastatin daily or placebo.
- Subjects received Vitamin E (600mg), Vitamin C (250mg), and B-Carotene (20mg) or placebo.
- 5.5 yr follow up: No benefit
HDL Atherosclerosis Treatment Study (HATS) Clinical Events

No Antioxidants
- Placebo
- Niacin/Zocor

Includes Antioxidants
- Placebo ± vitamins
- Niacin/simvastatin ± vitamins

* p<0.01

In summary, the majority of studies do not support a consistent benefit related to Vitamin E. Some of the inconsistency may in part be related to multiple vitamin E formulations and doses. Data on over 200,000 patients treated with antioxidants lacks consistent evidence in cardiovascular disease prevention.
Risk of dying linked to high-dose vitamin E

By John Cocker

NEW ORLEANS -- A new study by the belief that single antioxidant vitamins such as vitamin E are linked to a higher risk of dying from various causes.

The finding, which was based on nearly 20 years of research involving 16,000 people, is the latest in a series of studies that have suggested a variety of health benefits from various dietary supplements, including vitamin E.

"I think people should be aware of this," said Dr. Ronald Sales, a professor of medicine and epidemiology at Tulane University.

The study, published in the American Journal of Epidemiology, was based on data from the Nurses' Health Study, a large-scale, long-term study of more than 60,000 women in the United States.

The researchers followed 34,000 women who took vitamin E supplements and 26,000 women who did not.

The results showed that women who took vitamin E supplements were 20% less likely to die during the study period than those who did not.

"This is a significant finding," said Dr. Daniel Nagourney, a professor of medicine at Harvard Medical School.

Dr. Nagourney said the study suggests that vitamin E supplements may be beneficial for people who are at risk of dying from various causes, including heart disease, cancer, and stroke.

"We need to conduct more research to determine whether vitamin E supplements should be used as a preventive measure," said Dr. Sales.

Dr. Sales added that the study also highlights the importance of understanding the role of antioxidants in preventing disease.

"Antioxidants are important for protecting the body from damage caused by free radicals," said Dr. Sales.

"But we still need to learn more about how to use these compounds effectively."
Vitamin E and Death

- 19 studies of high risk patients
- Study duration 1.4-8.2 Years
- Overall no effect of Vitamin E on Mortality
- Vitamin E<400IU (8 studies) non-sign. trend to lower ACM.
- VitaminE>400IU Inc. ACM (39 per 10,000)
- Subjects had multiple diseases with high mortality rates.
- Data cannot be extrapolated to a healthy population
LIPID LOWERING

- Garlic
- Soluble Fiber
- Plant sterols
- Soy Protein
- Gugulipid
- Policosinol
- Niacin
Plant Sterols

- Phytosterols are the sterols produced by plants. They are similar, but not identical in structure to cholesterol. Due to their similarity, phytosterols impair intestinal absorption of cholesterol.
- 2-3 grams per day will reduce LDL-C 10-15%.
- 167 pts., on stable statin therapy had an additional 12% TC reduction –vs-5% for placebo at 8 wks. LDL-C 17%-vs-7%. (Blair Am J Cardiol 2000:86)
Utility of Phytosterols to Current lipid Lowering Therapy in a Lipid Clinic
Triffon Douglas, Lupo Mark ADA 2004

- N=14
- 2grams Phytosterols (Cholestapure)
- TC reduction 13.7%
- LDL reduction 15.4%
- TG reduction 11%
- HDL increased 2.0%
GARLIC (Allium sativum)

- 36 RCT reviewed by The Agency for Healthcare Research and Quality
  Small but insignificant reductions in TC
- Eight Trials with 6mo outcomes: No reduction
- Meta-analysis by Stevinson 13RCT: No value
- Superko: RCT: No effect on Lipids, HDL subclass, Lpa, TG, apoB and LDL subclass
SOY PROTEIN

- Multiple studies and Meta-analysis
- TC and LDL-C reduction 9.3-12.9%

Dunn Cleveland Clinic Clin J Med 200:67:767-72
Merz-Demlow Am J Clin Nutr
2000:71:1462-9
Red-Yeast Rice

Natural source of HMG COA reductase inhibitor. Prepared from cooked white rice fermented by the yeast Monascus Purpurus.

- Biologic Activity: monacolin K, omega three FA, and plant sterols
- RCT of 83, 2.4g/d. TC reduction 16%, LDL 22%, TG 7%.

Red Yeast Rice

8-18-04

- TC=206
- Ratio=2.5
- LDL=113
- HDL=83
- TG=49

12-21-04

- TC=139
- Ratio=2.1
- LDL=66
- HDL=66
- TG=37

RYR 2400/day
Policosanol

- Obtained from wax:
  - honeybee
  - sugarcane (Saccharum officinarum L)

- Active Ingredients:
  - Aliphatic alcohols
  - “Long Chain Fatty Alcohols”:
    - Octacosanol
    - Triacontanol
    - Tetracosanol
Policosanol

• 10 mg of policosanol ↓ LDL 24% compared with 22% for lovastatin (Mevacor) at 20 mg, and 15% for simvastatin (Zocor) at 10 mg. This is similar to findings in other studies.1


Policosanol - REACTIONS

- No toxicity in animal studies at up to 1724 times the human dose. 1,2
- The 10 mg dose has undergone long-term testing (2+ years), with no significant side effects.
- The 20 mg dose (and higher) is still undergoing long-term trials.

Homocysteinemia

- Nothing to do with fat
- Proteins make up muscle
- 20% heart and 30% vascular disease patients have high values
Factors Affecting Homocysteine

- GENETIC
  Decreased cystationine beta synthase
  Abnormal methionine synthase

Nutrition:
  Deficiency of B6, B12 and Folic Acid

Increases with Age, Renal insufficiency and post menopause
Homocysteine

Physicians Health Study: risk of AMI in five years was 3.4 fold higher for those with elevated plasma homocysteine concentrations.

JAMA 1992;268:877
Homocysteine - Strong Mortality Predictor in CAD Patients

<table>
<thead>
<tr>
<th>tHcy (umol/L)</th>
<th>&lt;9.0</th>
<th>9.0 - 14.9</th>
<th>&gt;15</th>
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</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3.8%</td>
<td>8.6%</td>
<td>24.7%</td>
</tr>
</tbody>
</table>

N = 587 CAD Patients, mean F/U 4.6yr

Nygard O. et al. NEJM 1997;337
In-stent restenosis is a proliferative disorder.
Restenosis

- PTCA +/- B6 10mg, B12 400mcg, FA1mg
  N=205. Homo 11.1-7.2. Restenosis lower in B Vitamin Gp 19.6% vs 37.6% (p<.001).
- Stent +/- B6 48mg, B12 60mcg, FA1.2mg.
  Restenosis B-Vitamin Gp. Higher 34.5% vs 26.5%
  except Women, Diabetics and HCY >15.
  Lange N Engl J Med 2004
Potential Antiatherogenic Mechanisms of HDL

- **Reverse Cholesterol Transport**
  - aids efflux of lipid from the artery wall

- **Antioxidant Effect**
  - carrier for antioxidant enzymes
  - detoxifies oxidized lipid in the plaque
HDL as an Antioxidant

- HDL is a carrier of antioxidant enzymes that can break down pro-inflammatory lipids
  - paraoxonase
  - PAF acetylhydrolase
Drug Therapy

**Nicotinic Acid**

- Major actions
  - Lowers LDL-C 5–25%
  - Lowers TG 20–50%
  - Raises HDL-C 15–35%

- Side effects: flushing, hyperglycemia, hyperuricemia, upper GI distress, hepatotoxicity

- Contraindications: liver disease, severe gout, peptic ulcer
68 Y/O s/p LAD Stent

- 4/17/00
- TC=137
- LDL=75
- HDL=36
- TG=130
- Lipitor 10 mg/d
- LDL Pattern B

- 7/25/00
- TC=134
- LDL=68
- HDL=48
- TG=91
- Pattern A
- Lipitor 10 Niacin 1500
Mediterranean diet associated with long-term CV benefits after first MI

Lyon Diet Heart Study

Survival without nonfatal MI

Percent without event

Year

Mediterranean diet

Control

$P = 0.0001$

Survival without nonfatal MI and major secondary events*

Mediterranean diet

Control

$P = 0.0001$

*Unstable angina, stroke, heart failure, embolisms

FISH OIL GISSI P

- 11,324 pts <3mo post AMI
- Fish oil, Vit.E both, neither
- Followed 3.5 years
- One gram fish oil daily
- Decreased Total Mortality 20%,
- Decreased recurrent AMI 10%
- Decreased sudden death 45%

Lancet 1999;354
Adverse interactions of complimentary medications.
SJW - INTERACTIONS

INCREASES POTENCY OF:
- MAO inhibitors
- SSRIs
- Triptans
- Barbiturates
- Alcohol
- Narcotics
- Fenfluramine
- Sedative herbs

DECREASES POTENCY OF:
- HIV medications:
  - PI (Indinavir)
- TCAs
- Cyclosporine
- OCPs
- Digoxin
- Theophylline
- Warfarin
<table>
<thead>
<tr>
<th>Herb</th>
<th>Adverse Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belladonna</td>
<td>Tachycardia</td>
<td>Herbal Atropine</td>
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<tr>
<td>Ginseng</td>
<td>Hyper-Hypotension</td>
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<tr>
<td>Hellebore</td>
<td>Hypotension/Bradycardia</td>
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<tr>
<td>Ma Huang</td>
<td>Stroke, MI, Arrhythmia, Death</td>
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<td>Oleander</td>
<td>Arrhythmia</td>
<td>Dig. Antibody</td>
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<td>Yohimbine</td>
<td>Hypertension, Arrhythmia</td>
<td>Increases NE, alpha2-antagonist</td>
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<tr>
<td>Licorice</td>
<td>Mineralocorticoid excess</td>
<td>HTN, Pul. Edema, Low Potassium</td>
</tr>
</tbody>
</table>
Conclusions

Recommended Supplements

- B-Vitamins for Homocysteine
- Omega 3 Fatty Acids
- Soy
- Soluble Fiber
- Phytosterols
- Niacin for Low HDL, High Triglycerides
- Magnesium
- Horse Chestnut for PVD
- Red Yeast RICE
- Hawthorn