Herbal Products and Cardiovascular Disease

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Objectives

- Review prevalence of use of complimentary and alternative medication (CAM) and general concepts surrounding use
- Discuss evidence for cardiovascular effects of selected CAM therapies (natural products)
- Review CAM with potential cardiovascular side effects
- Discuss common cardiovascular agents for which drug interactions would be a concern with CAM

A 64 year old man with CAD s/p MI and DES placement, HF with EF 20% comes to the office for an initial visit. He is partially adherent to conventional secondary prevention therapy (clopidogrel, ASA, ACE inhibitor, furosemide, niacin, folic acid), however has intolerances to statins and does not like side effects of beta-blockers. He is very interested in natural therapies and has brought a list of medications he is taking from the internet. These include hawthorn, red yeast rice, and bitter orange (for weight loss). He is also considering chelation therapy.

How do you approach this patient's conventional and alternative medicine therapies?

Definition of CAM

- Use of alternative therapies to prevent or improve a medical condition
  - Herbal medications (nutriceuticals)
  - Vitamins/Megavitamins
  - Mineral supplements
  - Nutritional components
    - e.g. antioxidants, soluble fiber, soy, stanols/sterols
  - Relaxation techniques
  - Accupuncture
  - Massage therapy

Definition of CAM

- Conventional Medicine
  - Practiced by traditional medical professionals (MD, DO, RN, PT, RPh)
- Complementary Medicine
  - Using some CAM techniques together with conventional medicine
    - Accupuncture for pain control, smoking cessation in addition to traditional pharmacotherapy/behavioral therapy
    - Deep breathing relaxation techniques for anxiety
- Alternative Medicine
  - Use of CAM *instead of* conventional medicine
- Integrated Medicine
  - Use of high-quality, evidence-based CAM in addition to conventional medicine

National Center for Complimentary and Alternative Medicine. http://nccam.nih.gov/health/whatiscam. Accessed 3/17/13.

Benefits of CAM

- Adherence
- Nutritional support
  - Better dietary habits
- Improvements in lifestyle changes
  - Exercise, smoking cessation
- Non-pharmacological therapies (e.g. mind-body connection)

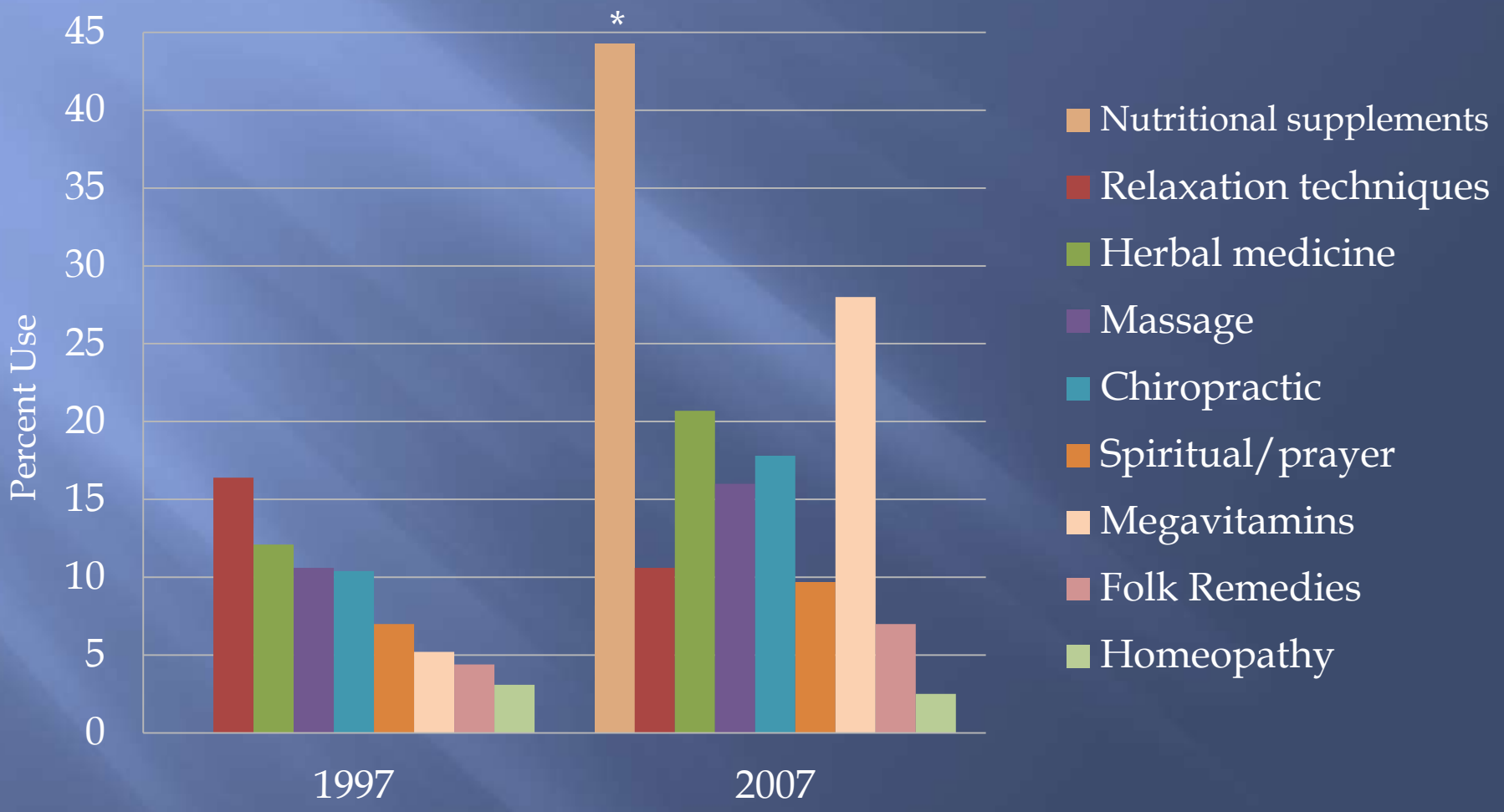
Prevalence of CAM

- Surveys indicate 40-70% of patients use some form of CAM
- Cuts across socioeconomic, age, gender strata
- Over $650 million spent on medicinal botanicals in 1998
- Multiple disease states
  - Pain, chronic diseases, digestive problems
- May be used in conjunction with traditional medical treatments
  - Only 40-50% of patients in surveys tell traditional health care providers about CAM
  - Drug interactions
  - Medication history

Cheung CK. *J Altern Complement Med.* 2007;13:997

Caufield JS. *Pharmacotherapy.* 2000;20:1289

Types of CAM Used



* Defined by NCCAM: herbal supplements, vitamins/minerals, probiotics, any OTC dietary supplement

Caufield JS. *Pharmacotherapy.* 2000;20:1289

Cheung CK. *J Altern Complement Med.* 2007;13:997

Patients' Reasons for Using CAM

- Perception that current therapy for condition is not adequately effective
- Cultural upbringing or ethnicity
- Desire to have more control over own health
- Links to cultural beliefs
  - Holistic health philosophy
  - Environmentalism
  - Strong internal locus of control
  - Transformational life experiences
- Studies have failed to show distrust in conventional medical system as a strong predictor

Caufield JS. *Pharmacotherapy*. 2000;20:1289

Conventional Medicine vs. CAM

Conventional Medicine	CAM
Randomized controlled trials demonstrating efficacy in treating a disease/disorder	Able to claim maintenance or improvement in health, not treatment of an ailment
Medicines prescribed by providers, dispensed from pharmacies	Recommended by alternative medicine specialist, herbalist, "nutritionist" – purchased OTC, health food store, internet site
FDA regulations – require patient information leaflets	"No side effects", but there are no required disclosures
Chemically/artificially manufactured	"All natural"
Pharmaceutical/Medical industry influence	Perception that there is no powerful industry supporting therapy

FDA Rules and Regulations Concerning Dietary Supplements

- Products are not regulated by FDA in the same way as drugs
  - Dietary Supplement Health and Education Act - 1994
  - Classified as dietary supplements
  - Limited claims for efficacy
  - GMP standards and product labeling are regulated
- Dietary supplement manufacturers cannot claim to "cure" or "treat" any medical condition, but can claim to maintain health
  - Can state "to maintain bone health" but not "prevent/treat osteoporosis"

Food and Drug Administration. www.fda.gov/RegulatoryInformation/Guidances/ucm144657.htm#iv . Accessed 2/28/13.
Food and Drug Administration. www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/RegulationsLaws/ucm110858.htm. Accessed 2/28/13.

FDA Rules and Regulations Concerning Dietary Supplements

- Manufacturer is responsible for ensuring safety of product prior to marketing
- FDA is responsible for ensuring post-marketing safety
  - Adverse reactions are reportable to MedWatch system
    - Plays an important role in regulatory monitoring
    - Dietary supplements allowed to remain on market as long as not proven unsafe or contain prescription drug entities
- Lack of product standardization

Miller LG. *Pharmacotherapy*. 2000;20:877.
Food and Drug Administration. www.fda.gov/RegulatoryInformation/Guidances/ucm144657.htm#iv. Accessed 2/28/13.

CAM Therapies for Cardiovascular Indications

Co-Enzyme Q10

- Pharmacologic properties
  - Cofactor involved in oxidative phosphorylation and generation of ATP
  - Free radical scavenger and anti-oxidant
  - High levels in heart, kidney, liver, pancreas
- Proposed cardiovascular effects
  - Hypotensive effects
  - Improve ventricular function (e.g. inotropy)
  - Improve tolerability of statins which may decrease concentrations

Vogel JHK. *JACC.* 2005;146:187.

Co-Enzyme Q10

	Proposed Mechanism	Evidence	Overall Conclusion
Dyslipidemia	Statin use decreases Co-Q10 levels, may decrease muscle metabolism, resulting in myopathy	Conflicting data: case reports, placebo RCTs, meta-analysis	Supplementation does not appear to decrease statin myopathy in RCTs
Heart Failure	Myocardial levels are decreased in HF and lower levels are associated with worse systolic function	Small trials, one large trial examined levels but not supplementation, meta-analysis	Supplementation may improve EF, but effect is diminished when used combination with ACEi

Chow SL. *Pharmacotherapy*. 2010;30:1e-49e.

Bookstaver DA. *Am J Cardiol*. 2012;110:526.

Co-Enzyme Q10

- Possible Adverse Effects
  - Minimal: GI
- Possible Drug Interactions
  - Monitor INR with warfarin
  - Monitor BP with anti-hypertensives

Natural Medicines Comprehensive Database. Co-Enzyme Q10 Monograph. Updated 10/2011.

Fish Oil (Omega 3 Fatty Acids)

	Proposed Mechanism	Evidence	Overall Conclusion
Arrhythmias	unknown	RCTs, meta-analysis	Small trials showed decrease in arrhythmia mortality, no benefit in larger trial or meta-analysis, proarrhythmia in patients with ICD
Heart Failure	Decreased cytokine mediators, anti-fibrotic effects	RCT (small)	Decreased time to death/HF hospitalization and arrhythmic death
Coronary Artery Disease	Triglyceride reduction, anti-inflammatory, antiplatelet effects	RCTs, meta-analyses	No mortality benefit in primary or secondary prevention. Decreased non-fatal events in secondary prevention.
Dyslipidemia	unknown	RCTs, case-control studies. Approved by FDA.	Effective in reducing triglycerides

Rizos EA. *JAMA*. 2012;308:1024

Chow SL. *Pharmacotherapy*. 2010;30:1e-49e.

Fish Oil

- Atrial fibrillation trials (AHA 2012)
  - No benefit in preventing postop atrial fibrillation (OPERA)
    - Preop loading, 2gm/day for 10 days postop
  - Neutral effect in preventing recurrent atrial fibrillation (FORWARD)
  - No increase in bleeding noted
- Possible Adverse Effects
  - GI distress, "fishy burp" – may take with food
  - Increased bleeding risk (high doses > 3 gm/day)
- Effective for reducing triglycerides, other hard endpoints have not shown benefit, but is well tolerated

Mozaffarian D. *JAMA*. 2012;308:2001-11.

Garlic

- Pharmacology
  - *Allium sativium,* allicin
  - Produce ACE inhibition and calcium channel blocking effects
    - Increase nitric oxide
    - Decrease LDL oxidation, inhibit LDL synthesis
- Decrease in BP (mean 8mmHg SBP)
- Inconsistent effects on LDL
  - Variability with formulation
  - Long acting formulations seem to have greatest benefit, fewest adverse effects
- Adverse effects – mild, primarily GI

Cicero AFG. *Curr Hypertens Rep.* 2013;epub 22 Feb 2013.

Chow SL. *Pharmacotherapy.* 2010;30:1e-49.

Gingko Biloba

- Pharmacology
  - Gingko leaf extract, multiple flavonoids (quercetin, isohamnetin, kaempferol, proanthocyanidins)
    - Mechanism unclear – potential anti-oxidant and anti-inflammatory actions
      - Inhibit platelet aggregating factor, thromboxane A2
- Peripheral vascular disease
  - Meta-analysis
    - Increase pain-free walking distance by mean 34m
  - RCT vs placebo in patients with ABI < 0.9
    - Trend to overall increase in pain-free walking distance
    - More significant increase in patients with shorter baseline walk distance

Chow SL. *Pharmacotherapy.* 2010;30:1e-49

Hawthorn (Crataegus)

- Extract of leaves/flowers/berries
- Pharmacology
  - Flavonoids producing ACE inhibition, phosphodiesterase type III/IV inhibition, Na+/K+ ATPase inhibition
- Case reports/small trials of short duration demonstrating both benefit and harm in HF
  - Worsening HF symptoms/hypotension
  - Modest improvements in HF symptoms, EF, exercise duration vs placebo – not in combination with traditional therapy

Chow SL. *Pharmacotherapy*. 2010;30:1e-49e.

Hawthorn in Heart Failure

Clinical Trial	Methods	Results
SPICE (Holubarsch, 2008)	RCT Primary endpoint: cardiac death, MI, HF hospitalization • N=2681 • NYHA class II-III HF • EF < 35% • Hawthorn extract vs placebo in addition to conventional HF therapies • 24mo f/u	No difference in time to first cardiac event No difference in adverse events Small decrease in sudden cardiac death in hawthorn group • Post hoc analysis • EF 25-35% subgroup • Event rate 5% vs 8.3%, HR 0.59, p=0.025
HERB-CHF (Zick, 2009)	RCT Primary endpoint: 6min walk • N=120 • NYHA class II-III HF • Hawthorn extract vs placebo in addition to conventional HF therapies • 6mo f/u	No difference in 6min walk No change in HR, BP No difference in QOL or symptoms Small benefit in EF in hawthorn group • Mean EF decrease in placebo 2%, no EF change in hawthorn, p=0.04 • No EF difference in subgroup with baseline EF < 40% No difference in cardiac adverse events

Holubarsch CJF. *Eur J HF.* 2008;10;1255.

Zick SM. *Eur J HF.* 2009;11:990.

Hawthorn (Crataegus)

- No benefit in RCT in HF when added to conventional HF therapy
- Minimal adverse effects
  - GI distress, bradycardia, hypotension
  - No significant increase in cardiac adverse effects over placebo
- Drug interactions
  - Theoretical interactions (additive effects) with beta-blockers, CCBs, nitrates, PDE 5 inhibitors
  - No significant interactions in clinical trials
  - Pharmacokinetic study demonstrating no significant interaction with digoxin

Chow SL. *Pharmacotherapy.* 2011;31:208e-271e
Natural Medicines Comprehensive Database. Hawthorn Monograph, Updated 9/2011.

Horse Chestnut (*Aesculus hippocastanum*)

- Chronic venous insufficiency
- Pharmacology
  - Seed extract contains escin
    - Inhibit elastase and hyaluronidase
    - Enzymes which are involved in leukocyte activation which results in vascular damage
- Meta-analysis of RCTs
  - Overall horse chestnut provides benefit over placebo (with or without compression stockings).
    - Pain reduction
    - Edema, leg circumference
- Well tolerated, minimal side effects
  - GI, pruritis

Pittler M. *Cochrane Rev*. 2012. Nov 14:11;CD003230

L-Arginine

- Semi-essential amino acid
  - Found in red meat, fish, poultry, dairy
- Pharmacology
  - Substrate for nitric oxide synthesis in vascular endothelial cells
  - In vitro and animal data demonstrate improved endothelial function, coronary and peripheral arterial vasodilation
- Well tolerated with few adverse effects
- Theoretical drug interactions with nitrates, PDE 5 inhibitors

Vogel JHK. *JACC*. 2005;146:187.

L-Arginine

	Evidence	Results
Heart Failure	Small RCTs with endpoints of renal function and radial artery vasodilation	Benefits on surrogate endpoints of vasodilation, but no large trials or benefits for hard endpoints
Coronary Artery Disease	Small RCTs in angina Large RCT post-MI • Stopped early due to excess mortality in L-Arginine arm	Inconsistent data in biomarker and angina improvement. Post-MI demonstrated no change in EF or vascular stiffness, increased mortality with L-Arginine
Hypertension	Meta-analysis, RCT	Significant decrease in BP (mean 5mmHg SBP) with L-Arginine, similar benefit in diabetic population.

Chow SL. *Pharmacotherapy.* 2010;30:1e-49e.

Cicero AFG. *Curr Hypertens Rep.* 2013;epub 22 Feb 2013.

Red Yeast Rice

- Naturally fermented rice product
  - Contains multiple plant sterols and monacolin substances which inhibit HMG CoA, as well lovastatin (monacolin K)
    - FDA called for removal of all products containing > 5mg of lovastatin
- Dyslipidemia
  - Significant decrease in LDL
  - Large RCT in Chinese population demonstrated reduction in cardiovascular events with highly purified formulation
  - Unclear if these benefits will be demonstrated in reformulated products

Chow SL. *Pharmacotherapy.* 2010;30:1e-49e.

Red Yeast Rice

- Adverse events
  - Similar to statins
    - Increase in CK, myalgias
  - Few reports of increase in liver enzymes
    - Most trials did not detect significant difference from control
- Drug interactions
  - Considered similar to those of statins
  - Additive effects with statins, niacin, fibrates
    - Risk of rhabdomyolysis or myalgias

Chow SL. *Pharmacotherapy*. 2010;30:1e-49e.

Chow SL. *Pharmacotherapy*. 2011;31:208e-271e

Folic Acid/B vitamins

- Coronary artery disease
- Pharmacology
  - Reduce homocysteine levels
  - May decrease smooth muscle proliferation, collagen synthesis, endothelial oxidative injury
- RCT Evidence
  - B vitamins/folic acid supplementation reduces serum homocysteine levels
  - Swiss Heart Study – early RCT with decrease in cardiac events with B vitamin/folate supplementation, primarily due to decrease in revascularization
  - Multiple subsequent large RCT show no impact on cardiac events

Vogel JHK. *JACC.* 2005;146:187.

Chow SL. *Pharmacotherapy.* 2010;30:1e-49e.

Vitamin D

- Cofactor in multiple processes in skeletal, vascular and cardiac muscle
  - Muscle cell proliferation and function in vascular, skeletal, and cardiac tissues
  - Anti-inflammatory effects
  - Decrease in renin-angiotensin activation
- Varying definitions – 25-OH Vitamin D levels
  - Normal: > 30 ng/ml (> 75nmol/L)
  - Insufficiency: 20-30 ng/ml
  - Deficiency: < 20 ng/ml (< 25 ng/ml in cardiovascular trials)
- Supplementation
  - Ergocalciferol (vitamin D, vitamin D2)
  - Cholecalciferol (vitamin D3)
  - Calcitriol (1,25 [OH]2 vitamin D) – activated form

Gupta A. *Atherosclerosis*. 2011;215:23-9.

Motiwala SW. *Curr Hypertens Rep*. 2012;14:209-18

Vitamin D

	Evidence	Results
Heart Failure	Small RCT, case control	Vitamin D supplementation improved cytokine profiles, lower 25-OH-vitD levels associated with higher CV events. No data that supplementation improves outcomes.
Coronary Artery Disease	Large RCT (WHI), cross sectional study	No benefit in calcium/vit D supplementation women in CV events. Epidemiologic analysis shows higher risk of first CV event in hypertensive patients with low 25-OH-vitD levels.
Hypertension	Cross sectional studies, large RCT (WHI), small RCT, meta-analyses	Lower 25-OH-vitD levels associated with higher BP and subsequent HTN. Conflicting results in supplementation on BP. • Large trial showed no impact on HTN with calcium/vit D. • Conflicting data from meta-analyses • Some indication of lower BP in hypertensive patients with vitamin D supplementation
Dyslipidemia	Case control, small RCT, epidemiologic studies	Conflicting data on association between low vitamin D levels and statin myopathy. Repletion in small trial improved statin tolerability.

Gupta A. *Atherosclerosis*. 2011;215:23-9.
Chow SL. *Pharmacotherapy*. 2011;31:208e-271e
Motiwala SW. *Curr Hypertens Rep*. 2012;14:209-18.

Vitamin E

- Coronary artery disease
- Antioxidant
- Epidemiologic trials suggested primary prevention benefit in CV events
- RCTs
  - No decrease in CV events with supplementation (primary or secondary)
  - Some trials show increase stroke or cancer risk when combined with beta-carotene

Vogel JHK. *JACC.* 2005;146:187.

Chelation Therapy

- EDTA infusions
- Proposed Mechanism:
  - Remove polyvalent cations (calcium)
  - Regression of atherosclerotic plaques
- Case reports/small studies showing benefit but others with negligible effects
- Risks identified in Cochrane Review
  - Also binds iron and other cations
  - Common side effects: GI, hypotension, exfoliative dermatitis
  - High doses or rapid infusions can cause nephrotoxicity or death

Vogel JHK. *JACC.* 2005;146:187.

Natural Medicines Comprehensive Database. EDTA Monograph. Updated 4/2012.

Chelation Therapy

- Trial to Assess Chelation Therapy (TACT)
  - Funded by NHLBI and NCCAM
- 2x2 factorial design
  - EDTA vs placebo infusions – 40 infusions, 3h each
    - Max 3gm EDTA, with 7gm ascorbic acid, electrolytes
  - Vitamins vs placebo
- Primary composite endpoint
  - All-cause mortality, MI, stroke, coronary revascularization, angina hospitalization
- Methodologic issues with study
- 1708 patients, all > 6months post MI
  - 65% completed all 40 infusions
  - 32% with diabetes
  - 80% had no angina symptoms at baseline

Lamas G. AHA Scientific Sessions 2012

Mark D. AHA Scientific Sessions 2012

Chelation Therapy

	RRR	CI	P value
Composite Endpoint (Overall)	18% (HR 0.82)	0.69,0.99	0.035
Composite Endpoint (Diabetics)	39%		0.002

* Data not yet fully published

- Overall decrease in composite endpoint in EDTA vs. placebo
  - 39 events, 60 months
  - Greatest contributor to composite was coronary revascularization
- No difference in any QOL measures
- No impact of high-dose vitamins on composite endpoint
  - Trend toward greater benefit in vitamin/chelation arm
- Authors' conclusions:
  - Appears safe
  - Hypothesis generating

Lamas G. AHA Scientific Sessions 2012
Mark D. AHA Scientific Sessions 2012
Lamas G. ACC Scientific Sessions 2013

Herbal Therapies with Potential for Adverse Cardiovascular Effects

Weight Loss Therapies

- Stimulant properties
  - Caffeine analogs
  - Ephedra-like agents
  - Increase BP, increase cardiac work, arrhythmia risk
- Diuretic properties
  - Volume depletion
  - Enhanced effect of thiazides or loop diuretics
  - Electrolyte disturbances

Cardiovascular Adverse Effects

STIMULANT PROPERTIES

- Bitter Orange (Zhi Shi, *Citrus aurantium*)
- Caffeine/Caffeine analogs
  - Cola nut
  - Guarana
  - Guar gum
  - Coffee
  - Tea/green tea
  - Wahoo root bark
  - Yerba Mate
- Capsicum
- Ephedra
  - Country mallow (Heartleaf)
  - Ma Huang
- Khat

DIURETIC EFFECTS

- Buchu (*Barosma*)
- Guarana
- Guar gum
- Horsetail
- Ilex
- Nettle
- Sorrel
- *Uzara* root
- Woodruff (*Asparula odorata*)

Chow SL. *Pharmacotherapy.* 2011;31:208e-271e

Vogel JHK. *JACC.* 2005;146:187

Herbs with Cardiac Glycoside Activity

- Black Hellebore (Christmas rose)
- Lilly of the valley (*Convallaria*)
- Night Blooming Cereus (*Cactus grandiflorus*)
- Motherwort
- Oleander
- Strophanthus
- *Uzara*

Vogel JHK. *JACC.* 2005;146:187
Natural Medicines Comprehensive Database

Tachjian A. *JACC.*2010;55:515.

Other Cardiovascular Effects

ARRHYTHMIAS

- Tachyarrhythmias
  - Aconitum
  - Guarana
  - Guar gum
  - Horny goat weed (*Epimedium*)
  - Kelp (Bladderwrack, *Fucus, Ascophyllum*)
  - Sparteine (Scotch Broom)

VASOCONSTRICTORS/ HYPERTENSION

- Blue Cohosh
- Butcher's Broom, Scotch Broom (*Cystius scoparius*)
- Yohimbine

NEGATIVE INOTROPES

- Butcher's Broom, Scotch Broom
- Khella (*Ammi visgnaga*)
- Lycium
- *Rauwolfia*

Tachjian A. *JACC*.2010;55:515.
Vogel JHK. *JACC*. 2005;146:187
Natural Medicines Comprehensive Database

Increase Bleeding Risk

- Bilberry
- Chamomile
- Curbicin
- Danshen (*Salvia miltorrhiza*)
- Dong Quai (*Angelica*)
- Feverfew
- Fenugreek
- Garlic
- Ginger
- Glucosamine
- Guggulipid
- Horny goat weed (*Epimedium*)
- Horse chestnut
- Kelp (Bladderwrack, *Fucus, Ascophyllum*)
- Licorice
- Motherwort
- Omega 3 Fatty Acids
- Policosanol
- Reservatrol (grape seed extract)
- Saw Palmetto
- *Tussilago farfara* (Coltsfoot)
- Willow
- Wintergreen
- Woodruff (*Asperula odorata*)
- Yohimbine

Chow SL. *Pharmacotherapy*. 2011;31:208e-271e
Vogel JHK. *JACC*. 2005;146:187
Taylor DM. *Pharmacotherapy*. 2006;26:634.
Tsai HH. *Int J Clin Pract*. 2012:66;1056-78.

Conflicting Data

BLOOD PRESSURE EFFECTS

- Ginseng
  - Various varieties
  - Both hyper and hypotensive effects reported
  - Palpitations or tachyarrhythmias (high doses)
  - Overall cardiovascular effects of ginseng appear minimal
    - Caution warranted in uncontrolled HTN, low baseline BP, or serious arrhythmias

BLEEDING RISK

- Gingko Biloba
  - Most databases and review articles list as possible adverse event
  - Numerous case reports, often with multiple factors associated with bleeding
  - Meta-analysis did not find that bleeding risk increased when considering study bias

Chow SL. *Pharmacotherapy*. 2011;31:208e-271e

Kellerman AJ. *Pharmacotherapy*. 2011;31:490.

Natural Medicines Comprehensive Database. Panax Ginseng Monograph, Updated 12/2012; Siberian Ginseng Monograph, Updated 8/2012; Gingko Monograph, Updated 8/2012.

Drug Interactions with Cardiac Medications

- Warfarin
  - Increase bleeding risk
  - Metabolic interactions from CYP P450 induction/inhibition
- Antiplatelet therapies
- Digoxin
  - Increase levels
  - Potentiate effects
  - Hypokalemia
- Potassium alterations
  - Hypokalemia
    - Licorice
    - Aloe vera
    - Gossypol
  - Hyperkalemia
    - Dandelion
- Cytochrome P450 inducers (inhibitors)

Chow SL. *Pharmacotherapy*. 2011;31:208e-271e
Vogel JHK. *JACC*. 2005;146:187
Tachjian A. *JACC*.2010;55:515.
Tsai HH. *Int J Clin Pract*. 2012:66;1056-78

Cytochrome P450 Interactions

INDUCERS

- Danshen
- Guggulipid
- St. John's Wort

INHIBITORS

- 2C19/2C9 (clopidogrel, warfarin)
  - Devil's claw
  - Gingko biloba
  - Lycium
- 2D6 (antiarrhythmics, beta-blockers)
  - Black cohosh
  - Gingko biloba
- 3A4 (warfarin, statins, CCB)
  - Devil's claw
  - Echinacea
  - Reservatrol (grape seed extract)

Chow SL. *Pharmacotherapy.* 2011;31:208e-271e
Tachjian A. *JACC.*2010;55:515.
Vogel JHK. *JACC.* 2005;146:187
Tsai HH. *Int J Clin Pract.* 2012:66;1056-78

Approach to CAM in Conventional Medical Setting

- Discuss patient's goals of therapy
  - What are advantages of CAM (from patient's perspective)
- Avoid referring too much to large clinical trials
  - Make discussion patient-centric and patient-specific
- Thoroughly review specific products patient has identified as beneficial
  - Offer resources where you found information

Back to the Case…

- Medication history is first step
  - Ask patient to bring actual bottles of supplements to review contents of proprietary formulations
- Ask to see literature provided to patient
- Review databases or resources
  - Clear adverse effects including ACS with bitter orange
  - Other agents have some possible benefit, discuss risks
- Consider patient's willingness to be adherent to traditional therapies
- Consider drug interactions

Resources

- Natural Medicines Comprehensive Database
  - Online database updated regularly (published by *Pharmacists Letter, Prescribers Letter*)
  - Complete monographs with evidence for safety, efficacy, drug interactions
  - Subscription required
- ACCF Complementary Medicine Expert Consensus Document. Vogel JHK, et al. *JACC.* 2005;46(1):184-221
  - Evidence for use
  - Tables of herbs/supplements with adverse CV effects

Resources

- Chow SL et al. Key Articles Related to Complementary and Alternative Medicine in Cardiovascular Disease
  - Bibliographies discussing clinical trial evidence
  - Part 1: Evidence for benefit of agents in CV disease
    - *Pharmacotherapy*. 2010;30(1)1e-49e

      http://www.pharmacotherapy.org/pdf/Key_Articles/Pharm3001e_Chow-CAM-KA.pdf
  - Part 2: Adverse effects and drug interactions related to CV disease
    - *Pharmacotherapy*. 2011;31(10)208e-277e

      http://www.pharmacotherapy.org/pdf/Key_Articles/Pharm3110e_Chow-CAM_pt2.pdf

Conclusions

- CAM has growing prevalence among patients, and some therapies have well established benefits or risks
  - Avoid discouraging use overall
- Few patients volunteer information about CAM
  - Include in standard medication history/ reconciliation
- Drug interactions and adverse effects with CV medications should be evaluated
- Resources are available to review constantly changing field of CAM and CV disease