JOHN
56 year old male, smoker, HTN, truck driver presents of ER with SSCP

A BROKEN HEART: TAKOTSUBO SYNDROME
TAKOTSUBO

- Acute MI presentation
  - acute emotional or physiologic stress, or life threatening illness
  - prognosis 95% survival
- Prevalence estimated: 0.2 to 4% of acute MIs
  - 88.8% are women, postmenopausal
- Hallmarks:
  - absence of obstructive CAD
  - LV mid to apical ballooning with hyperkinesis of base ("Octopus pot")
  - an apical sparing variant recently described
  - complete recovery 4-6 weeks

TAKOTSUBO PATHOPHYSIOLOGY

- Excessive vasoconstriction
- Impaired endothelium-dependent vasodilation
- Markedly elevated epinephrine and norepinephrine following mental stress when compared to "classic" MI (Martin et al JACC 2010; 56: 1840)
- Reported with pheochromocytoma, thyrotoxicosis, IV epinephrine, dobutamine stress echo, acute alcohol withdrawal, anesthesia
- Familial: mutation in gene FMR1 (Klinfeldt T et al Int J Card 2009; 137 (3))
- 21-50% have co-morbidities of depression and anxiety
- Recurrences occur: no data on prevention

TAKOTSUBO: REMAINING QUESTIONS

- Post menopausal women?
  - 80-90% female predominance; average age 57.7:
    - reduced estrogens and increased MVD
- Unusual contractile pattern?
  - higher density of beta-adrenergic receptors in apex; limited elasticity and coronary circulation in apex
- How to prevent?
  - no long term outcomes data; risk factors similar to CAD

HISTORY

- The dominant force in the whole body is that guiding principle which we term intellect or mind. This is firmly lodged in the midregion of the breast. Here is the place where fear and alarm pulsate. Here is felt the caressing touch of joy. Here then is the seat of intellect and the mind.
  - Lucretius, in The Nature of Things circa 55 BC

"Voodoo Death"
- Cannon, 1942
- Anecdotal experience of death from fright
- Deaths had several common features
  - Powerful external force, medicine man, wizard could cause demise
  - Victim was powerless
- Primitive and superstitious societies
- Postulated that death was from a lasting and intense response of the sympathetic/adrenal system
MODERN DAY “VOODOO DEATH/DISEASE”

- Medicine man or wizard
- Modern every day stress: acute and chronic
- Victim was powerless
- We cannot control our stress
- In primitive societies, death from “fright”
- Present here and now
- Takotsubo
- CHF, CHF, HTN, DM
- SCD
- Modern every day stress: acute and chronic

INTERHEART

- Landmark case control of first MI, 52 countries
- 11,119 MI (enrolled within 24 h of admit)
- 13,648 age matched controls
- Data collected: demographics, traditional risks and “psychosocial index” (depression, acute life event, stress at home/work/financial)
- 9 risks account for >90% of AMI; psychosocial index accounted for 32% of the risk

STRESS

- Stressor
- Disturbance that affects homeostasis
- Stress response
- Survival mechanism in the face of danger, or perceived danger
- Psychoneuroimmunology
- Emotions/Mind, nervous system, immune system

ANATOMY AND PHYSIOLOGY OF STRESS RESPONSE

- Hypothalamic-pituitary-adrenocortical (HPA) axis
- Autonomic nervous system
- Heart rate variability (HRV)
- Platelet receptors and/or reactivity
- Proinflammatory cytokines

HYPOTHALAMIC PITUITARY ADRENAL AXIS

- Hypothalamus releases corticotropin releasing hormone (CRH)
- The pituitary releases adrenocorticotropic hormone (ACTH)
- The adrenal cortex then releases cortisol
EFFECTS OF HPA ACTIVATION
- Cortisol (along with epinephrine)
  - mobilizes glucose, fatty acids, and protein
  - releases glycogen
  - suppresses the release of insulin
- Results in
  - a quick burst of energy,
  - improved memory functions,
  - decreased sensitivity to pain,
  - and a burst of increased immunity
- With chronic stimulation of HPA axis
  - hyperglycemia: hyperinsulinemia
  - hypercortisolemia: suppression of growth and sex hormones

AUTONOMIC NERVOUS SYSTEM
- Controls internal organs via effector neurons and circulating hormones:
  - Sympathetic: adrenal medulla releases catecholamines (ne;epi;dopa):
    - enhances cardiovascular function, increases blood flow to limb muscles, gastric secretions stop, pupils dilate
  - Parasympathetic: acetylcholine
    - blood flow is directed to digestive organs, HR decreases, pupils constrict

HEART RATE VARIABILITY (HRV)
- There is a normal beat to beat variation; with inspiration, vagus inhibited and HR increases
- In the young and healthy there is a high HRV
- HRV is affected mainly by the balance of the sympathetic and parasympathetic nervous systems
  - Sympathetic: low HRV, low frequency oscillations
  - Parasympathetic: high HRV, high frequency oscillations

EMOTIONS AND HEART RATE VARIABILITY
- Sympathetic: inflammatory response
  - Endothelial cells, fibroblasts, macrophages: release cytokines: IL-1, IL-6, Tnf alpha
  - Acute phase proteins, crp, fibrinogen
  - pro-coagulant and thrombotic state
  - "Sickness behavior" (fatigue, anorexia, anhedonia)
- Parasympathetic: anti-inflammatory:
  - Inactivates macrophage release
- Abnormal HRV:
  - Increased IL-6 and c-reactive protein

EMOTIONS AND PLATELETS/COAGULATION
- Platelets contain adrenergic, serotonergic, and dopaminergic receptors.
- Circulating catecholamines activate platelet alpha-2 adrenoreceptors:
  - initiate the thrombotic process
  - stimulate lipoprotein uptake by macrophages
  - mediate vasoconstriction through thromboxane A2, platelet activating factor, and 5-hydroxytryptamine (serotonin)

EMOTIONS AND INFLAMMATION
- Sympathetic: inflammatory response
- Endothelial cells, fibroblasts, macrophages: release cytokines: IL-1, IL-6, Tnf alpha
  - Acute phase proteins, crp, fibrinogen
  - pro-coagulant and thrombotic state
  - "Sickness behavior" (fatigue, anorexia, anhedonia)
- Parasympathetic: anti-inflammatory:
  - Inactivates macrophage release
- Abnormal HRV:
  - Increased IL-6 and c-reactive protein
THE STRESS RESPONSE IS:

- Lifesaving
  - Fleeing saber tooth tiger or lecturing to AzCIM graduating class
- Promotes beneficial adaptive behavior: avoid saber tooth tiger habitat, stop smoking, exercise, take up meditation
- Deleterious
  - Minor stressors are major catastrophes
  - Repeated exposure: feeling of surrender, helplessness, depression
  - Chronic stress:
    - Downregulates the immune system: increased inflammation and illness
    - Increases catabolic hormones: hyperglycemia, HTN, dyslipidemia

CHRONIC STRESSORS

- All the following are associated with adverse cardiac outcomes:
  - Low socioeconomic status:
    - Less cortisol variability (sign of HPA axis dysfunction)
  - Work stress:
    - Studied mostly in men
  - Marital stress:
    - Studied in women; increased carotid artery plaque; increased recurrent cardiac events
  - Social isolation:
    - Adverse cardiac outcomes in healthy and those with CAD
  - Caregiver strain
    - NHS; recurrent cardiac events

- Rozanski et al. JACC 2005;45:637-651

NEGATIVE AFFECTIVE STATES AND HEART DISEASE

- Depression
- Anxiety
- Anger

DEPRESSION STATISTICS and ACUTE MI

- Depression an independent risk factor for CHD: 1.6 times the risk
- Depression 3 times more common in the post ACS/MI than general population; prevalence of major depression 20-44%
- Depression higher in women than men
- Depression associated with high risk behaviors and non compliance
- Risk is dose dependent
- After acute MI depression doubles risk of recurrent CVD event within 1 to 2 years

- Lichtman et al, Circ 2008;118:1768-75

ARE WE DOING A GOOD JOB TREATING DEPRESSION IN CAD?

- 1,182 consecutive patients with ACS
- 17.6% of patients had moderate to severe depression
- Review of hospital records:
  - Treating physicians recognized depression in only 24.5% of these patients

- Amin et al. Am J Cardiol 2006;152:928-34

TREATMENT OF DEPRESSION IN CHD

- Beta blockers
- Antidepressants
- Psychological intervention
- Cardiac rehabilitation
- Exercise
- Vitamin D
- Meditation
- Connectedness
**PSYCHOSOCIAL INTERVENTION**

**RC TRIAL CHD**
- Reduced CVD events
- Recurrent Coronary Prevention Project
- 40% reduction MI and CV death
- Ischemic Heart Disease Study (only men)
  - 47% reduction CV death; no reduction in non fatal MI
- Randomized Trial F/U to IHDS
  - Higher mortality in women; no harm or benefit in men
- ENRICHD both treatment and control groups had successful reductions of depression (SSRI used in both groups)

**WHAT IS THE INTEGRATIVE APPROACH? TREAT THE PATIENT AS AN INDIVIDUAL: COPES**
- Coronary Psychosocial Evaluation Studies: 157 patients with ACS and depressive symptoms
  - 3 month observation period to exclude depression that may remit
  - 80 pts in “treatment group”
  - 77 usual care (treating physicians determined care)
  - Control group of 80 non depressed ACS
- Treatment group was collaborative allowing patients to choose either therapy and/or antidepressants and stepped care
  - Davidson et al Arch Int Med 2010;170:600-8

**COPES RESULTS**
- Patients in treatment arm were more satisfied with their depression care: 54% vs. 17% in the usual care
- MACE (nonfatal MI, hospitalization for ACS, and all-cause mortality) were significantly reduced in treatment arm compared to usual care arm: but absolute numbers of events were low (3 in treatment group and 10 in usual care)
  - Davidson et al Arch Int Med 2010;170:600-8
  - BUT 2 years later MACE was the same in the intervention and usual care groups; catch up phenomenon events were 3.4 times higher at 2 years: to be published

**MEN AND WOMEN ARE DIFFERENT**
- SWITCH Stockholm Women’s Intervention Trial for Coronary HD (F/U to IHDS higher mortality in women in the treatment group!)
  - 237 consecutive pts: AMI, CABG or PCI randomized to psychosocial intervention or usual care
  - Intervention group:
    - 20 small group sessions over 1 year; utilizing CBT; sessions last 2-2 1/2 hrs; by RN; educated patients regarding CVD risks
  - Mean F/U 7.1 years;
  - All cause mortality (no data on cause of death):
    - usual care: 25 of 125 died
    - intervention group: 8 of 112
  - 67% reduction in death in intervention group; differences in mortality could not be explained by other risks or variables

**CARDIAC REHABILITATION STUDIES**
- Meta-analysis of cardiac rehab concluded that when psychological stress was reduced:
  - cardiac mortality decreased by 34%
  - recurrent MI decreased by 29%
  - Dusseldorp Health Psycho 1999;18:506-19

**CARDIAC REHABILITATION**
- Prospective, observational study 701 patients: 20% were depressed on entry
  - 4 year F/U;
    - Depression decreased by 63% following completion of CR
    - Depressed patients that completed CR had a 73% reduction in mortality
  - Conclusion: CR was associated with both reductions in depression and excess mortality.
  - Unclear whether reduced mortality was related to improvement in fitness or reduction of depression.
  - Only 10-15% of eligible patients get to CR
EXERCISE

- Physical inactivity accounts for 25% of increased risk of CV mortality due to depression in older adults (CV Health Study n = 5000; mean age 72 yrs)
- Win et al. Heart 2011; 97: 500
- Lower depression scores are noted among those who are the most active in both healthy and ill cohorts
- Lawlor and Hopker BMJ 2001;322:763-7

VITAMIN D IN CV DISEASE

- 7,358 patients >50 years old with a CV diagnosis (included AF, PVD, CHF, MI, CAO); no prior depression; 1.1 year average f/u
- Vitamin D levels stratified into 4 levels:
  - Optimal >50 n=367
  - Normal 31-50 n=2,264
  - Low 16-30 n=3,402
  - Very Low </=15 n=1,325
- Compared to optimal levels, lower vitamin D levels were associated with increase in incident depression (independent of PTH and other risk factors)
  - N, HR 1.95 (0.99-3.87), P= .06
  - L, HR 2.15 (1.10-4.21), P=.03
  - VL, HR 2.70 (1.35-5.40), P= .005
- May et al. Am Heart J 2010;159:1037-43

MEDITATION

- Transcendental Meditation and SECONDARY PREVENTION

- 103 pts with stable CHD randomized to TM or “control”
- Within 16 weeks see improvements in BP, FBS and HRV
- Arch Int Med 2006; 166: 1218
- 201 black men and women with CHD randomized to TM or education
- In 5.4 year f/u 48%; risk reduction in mortality, MI and stroke and 24%; risk reduction in composite of CV events, BP, P/S stress
- Circ Cardiovasc Outcomes November 12, 2012

OTHER FORMS OF MEDITATION

- Review of literature: 813 studies that described meditation, more than 10 participants, and provided quantitative data on outcomes
- Most common categories of meditation:
  - Mantra
  - Yoga
  - Tai Chi
  - Mindfulness
  - Qi Gong
- Three most studied conditions:
  - HTN
  - CVD
  - Substance abuse
- Meta-analysis:
  - Qi Gong and Zen Buddhism reduced BP
  - Yoga reduced stress
  - Yoga and MBSR reduced anxiety in patients with CVD
SPIRITUAL ACTIVATION
- Controlled study, Japan: elderly >/= 87 with CHD, CVA or pulmonary disease
- Weekly, 30 minutes, chaplain sermons for 20 weeks; audience sang popular hymns before and after sermons
- Compared to controls, the 33 sermon attendees had
  - Improvement in proinflammatory cytokines
  - Fewer admissions from CVD or PD
  - Higher parasympathetic tone as measured by HRV
- Kurita A et al Int Heart J. 2011;52(5):299-303

POSITIVE WELL BEING
- Does emotional well being reduce CHD?

HAPPINESS AND CHD
- First study using prospective data: 6265 men and women, no CHD at baseline, from the NHANES 1 baseline interview 1971-1975:
  - Emotional vitality was measured: sense of energy and positive well-being and ability to regulate emotions
  - Incidence of fatal and non-fatal CHD event
  - Follow-up of mean of 15 years
  - Kubzansky and Thurston Arch Gen Psych 2007;64:1393-1401

HAPPINESS
- RR of CHD was 0.81 in those reporting high levels of emotional vitality after controlling for health behaviors and other CAD risks factors
- The attenuation of risk was “dose dependent”: RR of 0.93 in the medium emotional vitality and 0.81 in the high emotional vitality

IS THE GLASS HALF FULL?
- VA Normative aging study, prospective, 1306 men with no CHD at entry, 10 year f/u:
  - Those with highest levels of optimism had more than double the chance of NOT having a CHD event

SO WHAT CAN YOU DO?
- Recognize the positive and negative emotions in your patients
- Make sure your patients get to cardiac rehab programs: only 56% of eligible patients are referred
- Refer for behavioral therapy, exercise, meditation, psychotherapy
- SSRI some efficacy and safety in CHD: sertraline and citalopram
- Foster behavioral changes through motivational perspective; get patients to voice:
  - Own reasons for initiating change
  - Personal preferences
  - Sense of purpose
  - Coping strategies
ANN: 49 yo female presents to ER with chest pain

CP IN YOUNG FEMALE

- Anesthesiologist, physically very active developed substernal CP and SOB several hours prior to coming to ER, still having CP
- PMHx: breast implants, uterine fibroids; on no meds
- SHx: no drug, tobacco, alcohol
- CAD risks: NONE
- Labs normal
- Taken to cardiac cath lab

IHD IN WOMEN

- 500,000 women undergo coronary angiography annually:
  - 50% of women have "normal" coronaries or non-obstructive disease
  - 75% of men have "normal" coronaries or non-obstructive disease
  - Women with chest pain, evidence for ischemia by stress test or MI and normal or non-obstructive CAD by routine coronary angiography: have been reassured that they are FINE
- 1996 NIH launched WISE study: prospective; compared cardiovascular events and death in women referred for clinically indicated cardiac cath who had normal or non-obstructive (<50% stenosis) CAD with age matched controls

CORONARY MICROVASCULAR DYSFUNCTION

- Previously Syndrome X was thought to be benign.
- At least half of the women with normal coronaries or non-obstructive CAD have MVD.
- MVD causes myocardial ischemia and is not benign: 2.5% annual risk of CV event (including death, MI, stroke).
- Gold standard for diagnosis and risk stratification is the invasive coronary reactivity test that uses acetylcholine, adenosine and nitroglycerin:
  - Impaired endothelium dependent coronary reactivity: acetylcholine/nitroglycerin are infused and CFR and vessel diameter are measured; predicts adverse CV event. Circulation 2004; 109: 722-725
  - Impaired non-endothelium dependent coronary reactivity: adenosine (non- endothelium dependent microvascular dilator) is infused in coronary to measure CFR; predicts adverse CV event. J Am Coll Cardiol. 2010 June 22; 55(25): 2825–2832
WHY ARE WE TALKING ABOUT IHD IN WOMEN?

- Increase awareness that IHD differs in men and women

"Yentl Syndrome" 1991 Bernadette Healy published in NEJM under diagnosis and under treat women with IHD still need to close the gender gap!
- more high risk men than high risk women are prescribed aspirin, statins
- women with ACS are less likely than men to have cardiac cath or PCI even after adjusting for age and risk factors even though women and men derive the same benefit from PCI even though mortality rate is highest in those women NOT referred for PCI


INTEGRATIVE TREATMENT OF MVD

- Therapeutic lifestyle changes risk factors are the same for atherosclerosis and MVD.
- Holistic approaches are necessary and are being studied:
  - Arginine: precursor of nitric oxide; promotes release of nitric oxide and reduces endothelin (potent vasoconstrictor)
    - 1 gram TID and advance to 3 grams TID as tolerated
    - but increased risk of death following MI Circ 2003, 105 (5): 449
  - Acupuncture: trials may get underway next year: pilot study of TA vs. sham
    - Both improved symptoms but urinary cortisol levels lower in TA alone
  - Hypnosis: autogenic training consists of 6 standard exercises aimed at reducing autonomic anger and stress symptoms; study of 53 women with MVD underwent 8 week program had decreased symptom severity and frequency. Menopause 2009, 16: 60

WHAT GOES BUMP IN THE NIGHT

72 yo woman wakes up with a racing pulse and SOB

PMHx: HTN and dyslipidemia
Meds: metoproplol succinate 50 mg/ day. No OTC or supplements.
In ER: BP 160/90, pulse 132 irregular, RR 20, Temp 98.2, Ht 5’2”, Wt 182 lbs. BMI 33, otherwise PE unremarkable.
CBC, CMP, T2Ts U/A, troponin I, CMB normal.
Converted to NSR after IV diltiazem and was sent home.
WHEN I FIRST SEE AN AFIB PATIENT

- What are their risks?
- How can I keep them in NSR?
- Do they need anticoagulation?

OSA AND AF

- OSA directly related to BMI; 34% of obese have OSA.
- OSA and AF share many risk factors.
- Approximately half of patients with AF may have OSA.
- OSA predisposes to hypoxia, hypocapnia, increased sympathetic drive (during sleep and wakefulness) and pressor surges (ventilatory efforts against upper airway obstruction); all are a substrate for AF.
- Bidirectional: AF can increase episodes of OSA and Central Sleep apnea.
- OSA less likely to respond to AAD and ablation.

DOES TREATMENT OF OSA PREVENT ATRIAL FIBRILLATION?

- CPAP reduces hypoxia, inflammation, sympathetic overactivity and hypertension.
- No good prospective trials:
  - trial looking at recurrent AF 1 year after cardioversion:
    - 42% recurrence in treated OSA (n=22)
    - 82% in untreated OSA (n=27)
    - 17% in control group of AF patients, OSA status unknown (n=19)
    - Circ 2003 107(20):2589-94
  - 316 patients treated with CPAP found significant reduction in arrhythmias including AF during CPAP: Heart Vessels 2010 25:63-9
  - Tracheostomy in 10 patients with severe OSA, no recurrent AF in 6 months: Am J Cardiol 1983 52:490-4

ATRIAL FIBRILLATION RECURRENT AFTERABLATION

- 426 pts undergoing PVI: 62 had OSA, 32 CPAP users and 30 non CPAP users.
- CPAP resulted in higher AF free rate (72% vs. 37%).
- higher AF free rate off AAD or repeat ablation.
- AF recurrence 2.4 times higher in the CPAP nonusers.
  - JACC 2013;62:300-5

INTEGRATIVE TREATMENT OF AF

- PREVENT: CVD risk factors are associated with majority of AF; pharmacotherapy (next slide)
- TREAT:
  - keep in NSR / control heart rate: anti-arrhythmics, ablation
  - prevent stroke:
    - CHADS2: CHF, HTN, Age>75, DM, Stroke (2 pts). Score of 2 or more: warfarin or other anticoagulant; 0-1 ASA 81-325 mg
    - CHADS2VASC assigns a value of 2 if > 75, adds vascular disease, and sex (F=1); more valid to risk prediction for those who are deemed low or intermediate risk by CHADS2.
    - prevent HE: rate control if treatment or previous AF
INTEGRATIVE TREATMENT OF ATRIAL FIBRILLATION

PRIMARY PREVENTION

- RECENT: no large prospective randomized trials.
- PUFA: no meta-analysis data or large prospective trials.
- Retrospective data: positive effect in patients with PPM and post-ablation.

SECONDARY PREVENTION

- RECENT: no large prospective randomized trials.
- PUFA: no meta-analysis data or large prospective trials.
- Retrospective data: positive effect in patients with PPM and post-ablation.

INTEGRATIVE TREATMENT OF ATRIAL FIBRILLATION: ACUPUNCTURE

- Acupuncture: can acupuncture reduce the recurrence of AF post electrical cardioversion?
- 80 pts: 26 Amio; 17 ACU; 18 ACU sham; 24 Control
- 10 weeks of acupuncture starting 2 weeks post cardioversion patient follow-up for 1 year
- AF recurrence: 27% Amio; 35% ACU; 69% ACU sham; 54% Control

OTHER INTEGRATIVE APPROACHES TO AF

- Hypnosis: 50 consecutive pts undergoing CABG given pre-op hypnoidal explanation of surgery, matched to 50 controls undergoing CABG in same center; 3 cases of post-op AF in treatment group vs. 12 cases in control group (Circ Circ 2008; 114: 1455).
- Healing touch: 227 pts randomized to no, HT, and partial intervention (visitation): no decrease in use of pain meds or AF but decrease in anxiety scores and length of stay (J Altern Complement Therap 2008; 14: 244-7).
- Green tea: may reduce atrial fibrosis and may prevent AF occurrence and recurrence; epigallocatechin-3-gallate decreases inflammation, oxidation and matrix metalloproteinase activity (J Cell Biochem 2011; 112: 1709-12).

MIND-BODY AND ATRIAL FIBRILLATION

- Framingham data: anger, hostility, and tension in men significantly related to AF (and to CHD and total mortality) 10 year f/u (Circulation 2005; 67: 692-6).
- Stress is the most common triggering factor cited by patients hospitalized with AF.
- Pre-op depression, anxiety and general stress are associated with higher incidence of post CABG AF (Heart Lung 2011; 40:4-11).
- What is the treatment? Randomized trial of 117 pts scheduled to undergo CABG; 60 received holistic therapy of exercise and stress reduction; 57 in control group. No difference in AF rate but study follow-up was only 2 weeks. (BMC Complement Altern Med 2011; 11:20).

HOT OFF THE PRESS

- 3,530 enrolled in Framingham in 1979-1983 followed for 18 years
- Serum magnesium level in the lowest quartile (<1.77 mg/dl) was associated with a HR for atrial fibrillation of 1.54 after adjusting for BMI, ETOH, diuretic use, and potassium.
- Circulation 2012;Nov 21

AF CALCULATOR

http://www.framinghamheartstudy.org/risk/atrial.html#
Chief concern: His 66 yo father had an MI last month. Jacob rushed to his friend who is a cardiologist who did a nuclear stress test that was normal, but he was prescribed a statin “just for prevention.” Jacob is concerned and wants to see a natural approach. But he also is concerned about heart disease and wants a CT scan of his heart and ALL other tests that can be done. “I do not want to have a heart attack like my father!” He knows that 40-60% of all MI and SCD occur without warning!

SHx: never smoked; two martinis/day to relax after work; works as COO in hospital; divorced; runs marathons to keep himself “sane”; no religious affiliations and little time for friends or family.

PE: 138/90, 5ft 10 inches, 175 lbs. (BMI 25), unremarkable PE.

Labs: TC 180; HDL 42 LDL 123; TG 125. CMP, TSH, CBC all normal.

What is his risk for a cardiac event?

Framingham risk score (age, gender, cholesterol, HDL, SBP, tobacco): 3% risk of heart attack in the next 10 years

Framingham general CV risk score (adds diabetes to the calculation): 8.4% of CV event in next 10 years (includes PVD in addition to CHD)

AHA risk calculator: 3% risk of heart attack in 10 years (takes into account diabetes, BP, BMI and waist circumference, glucose intolerance)

ATP vs iPhone app: 9% (similar to AHA calculator)

Framingham: low < 10% risk of CHD in 10 yrs; intermediate 10-20%; high >/=20%.

WHAT ABOUT CHECKING A HIGH SENSITIVITY CRP?

Predicts future risk of CVD event independent of other risk factors: hsCRP > 3 a/w 60% increased risk in CHD as compared to <1 across all FRS

WHS: hsCRP is additive to LDL and Framingham risk score in predicting events

AHA and CDC recommend hsCRP to be used as a risk marker in FRS 10-20%

Low risk: <1 mg/L
Average risk: 1 to 3 mg/L
High risk: >3 mg/L

JUPITER:

RDBPC 17,802 men (>50 yrs) and women (>60 yrs) with LDL-C <130 mg/dL and hsCRP >2.0 randomized to receive placebo or 20 mg rosuvastatin: 50% and 37% reduction in LDL and CRP in treatment group

142 CV events in rosuvastatin group vs. 251 in placebo group (HR 0.56).

All groups benefited from statin regardless of age, gender, ethnicity, or risk factors.

NEJM 2008; 359:2195-2207

Limitations of hsCRP

Although hsCRP can raise risk estimates, it cannot rule out disease

Variability in levels based on ethnicity and gender: highest in AA>hispanics>whites>Asians;

Improvement in risk reclassification better in men than women

JUPITER had no low hsCRP treatment arm and therefore do not know that benefit seen is from hsCRP or that statins would benefit everyone

Causative role of hsCRP is being challenged: recent GWAS no relationship between genetically elevated hs CRP and CVD

How to treat high hsCRP

- Statins reduce hsCRP by 38%: protective effects of statins go beyond lipid lowering
- hsCRP and LDL is lowered patients fared better than when LDL alone was lowered.
- Decrease in ischemic events occur early after statin therapy before plaque regression.
- BMI is directly associated with CRP.
- Physical activity is associated with lower CRP.

- Whitehall observational study of 4,865 men and women for 10 years; 2.5 hours of physical activity associated with lower CRP and IL-6. Hamer M et al Circ 2012
- Low 25(OH)D Vitamin D levels are associated with higher sdLDL-C but not with higher hsCRP. Am J Med 2012; 8(3): 437-443
- Low dose aspirin has no effect of CRP. J Am Coll Cardiol 2001; 37(8): 2036-2041

WHAT ABOUT CHECKING VITAMIN D LEVEL?

- Deficiency is a risk for CVD.
- Framingham offspring study 1,327 participants, CVD was 2.7x-4.8x higher among those with low vitamin D levels. Circulation 117 (2008) 629-637
- NHANES III 15,344 for 2.5 years; those with lower quartiles (25th) had a 1.7x increased mortality compared to higher quartiles; mean mortality in those with level < 20 ng/ml. Arch Intern Med 2008; 168: 1629-1637
- Those raised from 20 to 125 had a reduced mortality. Prospective cohort study (n=10,418), low vitamin D was independently associated with all cause and CV mortality. Arch Intern Med 2008; 168: 1547-1553

- Does supplementation reduce risk?
- Meta-analysis of 16 randomized trials: those with low vitamin D levels 26% higher time to CV event. Low vitamin D was associated with increased mortality. J Am Coll Cardiol 2011; 58(15): 1547-1556

OTHER TESTING: CAC SCORE?

- Evidence: 3 large observational studies (MESA, Rotterdam, Heinz Nixdorf Recall Study)
- 10,000 asymptomatic people followed for median of 4.8 years: addition of CAC to Framingham risks significantly improved risk prediction of coronary events.
- 30%-52% of individuals initially at intermediate risk were reclassified into low or high risk with CAC.

LIMITATIONS OF CAC

- The calcification of plaque occurs late in the process and vulnerable plaques are not necessarily calcified. CONFIRM (79% vs 3.7% with CAC) had nonobstructive and obstructive CAD.
- Most of the studies are done in patients over the age of 50, but the process begins early in life: autopsy reveals that up to 60% of 30-39 year olds have plaques. JAMA 2001; 281: 727-735
- When do you repeat CAC? If 0? If following treatment with statins?
- If scan in men < 40; women < 50 due to very low prevalence of calcium.
- In patients with high suspicion for CAD, CAC did not predict need for revascularization. J Am Coll Cardiol 2008; 52: 877-884
- Although CAC is predictive, we need studies to determine if CAC score guided therapy affects clinical outcomes.

IMAGING THE FUTURE?
**CACs and treatment? Mayo clin proc “Neutralizing the effect...”**

- PMID: 23910408 [PubMed - in process]

**CORONARY CTA**

- CONFIRM: 14,000 symptomatic pts almost 2 yr f/u; CTA predicted mortality: 0.36% annualized mortality if no CAD vs 2.63% in those with obstructive CAD
- Meta-analysis of > 7000 men and women who had CTA for suspected CAD, followed for at least one year
- Significant stenosis (calcified or not) had a 10 fold higher risk of CV event; and 6 fold higher risk independent of calcification
- Any CAD carried a 4.5 fold higher risk for CV event

**WHEN SHOULD WE ORDER A CTA?**

- Consensus exists that the following applications are useful:
  - evaluation of acute chest pain in a stable patient: improves diagnostic accuracy of ruling out obstructive CAD and can alleviate need for invasive testing;
  - preoperative evaluation of cardiac patients undergoing non-cardiac surgery;
  - pts of cardiac transplant patients (most undergo coronary angiography yearly and most of these are negative);
  - pts of symptoms in CABG and post stent (larger stents) patients
- Asymptomatic high risk individuals: no studies linking treatment in those non-calcified, non-obstructive plaques to decreased events. 1 out of 5 low/moderate risk people have plaque???

**WHAT ABOUT THE RADIATION EXPOSURE?**

- Chest X-ray 0.1 mSv
- CAC score 0.6-1.5 mSv
- CTA of coronaries <3.0-4.2 mSv
- Coronary angio 8.5 mSv
- NST 6-17 mSv

**GENETICS**

- Reduction of risks such as HTN, smoking, high cholesterol have been associated with a 30% reduced risk. BUT
- 40-60% of risk is genetic
- 33 genetic variants are associated with increased risk for CAD:
  - 8 variants mediate risk through lipids; 2 through HTN
  - 23 loci act independently of known risk factors
- the increased relative risk for each variant varies from 0% to 97% with a mean increased risk of 18%
- the frequency in the population varies from 2% to 91% with a mean frequency of 47%

- J Am Coll Cardiol. 2012;60(18):1715-1721
BE VERY CAREFUL...

- SLO1B1 "helps predict statin induced myopathy"
- only simvastatin was used in studies with doses of 40 to 80 mg
- LPA Aspirin "predicts CVD risk reduction with aspirin" only carriers are helped with aspirin
- present in only 4% of population and mainly studied in women
- KIF6 "predicts CVD risk and risk reduction with atorvastatin and pravastatin"
- no validation on recent meta-analysis

WHAT WOULD I DO WITH JACOB?

- Additional possible tests:
  - Labs: hs CRP, vitamin D level.
  - CAC score.
- Treatment:
  - treat pre-hypertension/hypertension; continue statins if hs CRP is >1 or calcium is present in coronaries.
  - try to help him improve psychosocial aspects of lifestyle.

Thank you