Integrative Approaches to Cardiovascular Disease
Mimi Guarneri MD FACC

Unsustainable Costs: Unacceptable Outcomes

- 2.5 trillion spent in the current healthcare system
- 4.3 trillion by 2023
- 16% of nation’s GDP
- Double the amount of other western nations
- US ranked 37th in the world in health outcomes

Figure 1: Number of People Reporting Selected Chronic Diseases, 2003

Figure 5: Economic Impact of Chronic Disease, 2003

DATA WATCH
North America Makes Up Almost Half of All Global Pharmaceutical Sales

Source: 2006 data, IMS Health Inc.
What Really Causes Cardiovascular Disease?

MRFIT: Correlation Between Cholesterol Levels and CHD Death

35% of CHD Occurs in People With Total Cholesterol < 200 mg/dL

Residual Cardiovascular Risk in Major Statin Trials

EMERGING RISK FACTORS
- Apo B/ApoA1
- Inflammation
- Fibrinogen
- Methylation
- Insulin Resistance
- Lp(a)
- Low HDL 2B
- Small Dense LDL
- Increased PAI1
- Vitamin D Deficiency
- Adverse Childhood Events
- Increased Factor VII
- Increased Factor X
- Sedentary Lifestyle
- Central Obesity
- Toxins
- Depression
- Anger and Hostility
- Response to Stress
- Caregiver Role
- Social Isolation
- Social Support
- Purpose in Life
70-90% of chronic disease

What Really Determines Health or Disease for Most of Us?

Genetic Profiles
- Cholesterol Regulation: ApoE, CETP, SELE, Apo A-1, hepatic lipase
- Obesity: leptin receptor gene mutations
- Methylation: MTHFR
- Hypertension: GNB3, AGT, AGTR1
- Coagulation: Factor 2, Factor 5
- Reduction-Oxidation Balance:
  - CYBA Mutation A
  - CYBA Mutation B
  - KIF6 Statin Therapy
  - 9P21

Association of the Trp719Arg Polymorphism in Kinesin-Like Protein 6 With Myocardial Infarction and CHD in 2 Prospective Trials
The CARE and WOSCOPS Trials
JACC Vol51 No.4.2008
35 Polymorphisms evaluated recurrent Myocardial Infarction

Carriers of the Trp719Arg in KIF6 had a hazard ratio of 1.50 in CARE and an Odds ratio of 1.55 in WOSCOPS.

In CARE and WOSCOPS carriers of the 719Arg allele significantly benefited from Pravastatin with a risk reduction of 37%.

Noncarriers of KIF6 719Arg were not shown to have increased CHD event risk and received less benefit from intensive statin therapy in Prove-IT. Benefit of intensive statin therapy was six-fold greater in carriers than non carriers!

Rainbow the cloned cat and her mother - Think “Epigenetics”
NEGATIVE PREDICTIVE POWER EBCT

- 1764 persons EBT and Angiography
- Sensitivity for Obstruction (any Calcium) 99.4% in Men, 100% in Women
- Negative Predictive Power >99%

Haberl et al. JACC Feb 2001

Coronary Calcium
Progression of right coronary artery calcium score over 5 years

1993  
Calcium Score: 56  
Volume Score: 45

1995  
Calcium Score: 90  
Volume Score: 78

1997  
Calcium Score: 128  
Volume Score: 113

Rest-Stress Rb-82 PET (45 mCi)

Carotid Intima–Media Thickness (CIMT)

Mean CIMT 1.174 mm
LESSON 1:
More Plants Less Meat

“The China Project”
- A study looking at the rates of > 50 diseases in rural China vs. the U.S.
- Fat intake was twice as high in the U.S.
- Fiber intake was three times lower in the U.S.
- Animal protein intake was 90% higher in the U.S.
- Heart disease death rate was 16.7 fold greater for men and 5.6 fold greater for women in the U.S.
- Other diseases were also higher in the U.S.:
  - cancers
  - osteoporosis
  - diabetes
  - HTN
  - ref: Campbell, Parpia and Chen; Am J Cardiol, 1998, Nov 26

“A diet rich in fruits, vegetables and low fat dairy foods and with reduced saturated and total fat can substantially lower blood pressure.”

“Consumption of fruits and vegetables, particularly green leafy vegetables appears to have a protective effect against heart disease.”
LYON Heart STUDY
5 Yr.RCT 605 CHD
More Fruit
More beans
More Veggies
More Fish
Less Meat
No Cream
No Butter
Canola Oil

Compared with patients consuming the control diet, patients consuming the intervention diet had significantly reduced serum concentrations of hs-CRP, IL-6, IL-7, and IL-18, as well as decreased insulin resistance.

A Mediterranean-style diet might be effective in reducing the prevalence of the metabolic syndrome and its associated cardiovascular risk.

Esposito et al., JAMA 2004; 292

Among individuals aged 70 to 90 years, adherence to a Mediterranean diet and healthful lifestyle is associated with a more than 50% lower rate of all-causes and cause-specific mortality.


Lesson 2: Hara Hachi Hu
Increased Carbohydrate Calories
Source – CDC, 2004

* Between 1971 and 2000
  - women's daily intake of calories rose 22%, to 1,877 calories a day from 1,542
  - men upped their daily intake 7%, to 2,618 calories a day from 2,450
  - Most of the increase comes from eating more carbohydrates, the study said.

* Americans are still eating about the same total amount of fat and protein that they ate in 1971.
Fat is down, calories are up

- Average fat consumption is about 34% of total calories (from 42% in 1960s)
- However calorie consumption is dramatically higher (increased simple carbohydrates)
- Therefore total fat consumption is only modestly lower

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Pavlov's Dogs

- 54 percent of all Americans clean their plates even when they're full
- 39 percent eat when they see food
- 20 percent eat when depressed
- 19 percent keep eating until stuffed

Source: Prevention poll, Spring 1998

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Obesity Trends Among U.S. Adults 2003

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” person)

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Metabolic Syndrome

Unadjusted Kaplan-Meier Hazard Curves for CVD Mortality

JAMA 2002; 288: 2714
The Diabetes Explosion

The CDC predicts that if the current trend continues, 1 out of 3 children born in the year 2000 will be diagnosed with diabetes within their lifetime.

Childhood obesity is also rising at an alarming rate!

Adipose Tissue Distribution

ADIPOKINES

Atherosclerosis is an Inflammatory Disease

Inflammation is a Risk Factor for MI

Adapted from N Engl J Med 1997;336:973-979.
**Women’s Health Study: hs-CRP, Lipids, & Risk of Future CV Events**

Quartile of TC:

1. 0
2. 1
3. 2
4. 3
5. 4
6. 5
7. 6
8. 7
9. 8
10. 9

Quartile of hsof hs--CRP

Source: 

**PROVE IT TIMI 22**

Risk reduction with achievement of triple goal of LDL < 70 mg/dl, TG < 150 mg/dl, and HS-CRP < 2 mg/l

- LDL < 70 mg/dl = 28% risk reduction
- LDL < 70 mg/dl and TG < 150 mg/dl = 32% risk reduction
- LDL < 70 mg/dl, TG < 150 mg/dl, and HS-CRP < 2 mg/l = 41%

**Lesson 3: The Grapes of Life**

**Polyphenols**

- Tea
- Chocolate
- Coffee

- **Tea (Camellia sinensis)**
  - Tea = 2nd most consumed beverage in the world after water
  - > 1,000 types of tea on the market
    - White (buds and young leaves)
    - Green (steaming or panfiring)
    - Oolong (partial fermentation)
    - Black (fermenting)
  - High level of polyphenols
    - flavonoids, tannins, catechins

- **Preventive Medicine**
  - January 2003;36:64-70.

**Endothelial dysfunction associated with coronary artery disease (CAD) & increased oxidative stress**

- 66 patients with proven CAD has ultrasound testing after:
  - Short-term: 2 hrs after consumption of 450 mL tea or water
  - Long-term: 4 weeks after consumption of 900 mL tea or water daily

- Short & long-term tea intake:
  - plasma flavonoids & endothelium-dependent flow-mediated dilation of the brachial artery vs. water (P=0.001)
  - Caffeine (200 mg) had no effect on flow-mediated dilation

**Short- and Long-Term Black Tea Consumption Reverses Endothelial Vasomotor Dysfunction in CAD**

Those who consumed > 5 cups/d had a risk of all-cause and CVD mortality 16%-26% (compared with < 1 cup/d)

- Stronger association with women (? smoking)
- No association between green tea consumption and cancer mortality
- Iwai et al found mortality in Japanese which included CV and Cancer

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Supplements for Cardiovascular Disease
- Antioxidants
- Plant Sterols
- Soluble Fiber
- Vitamin D
- Omega 3 Fatty Acids
- B-Vitamins
- Minerals
- Herbs

Medicines from Plant Origins
- THE BARK OF THIS TREE CAN BE USED AS AN ANALGESIC:
  - WHITE WILLOW
  - ASPIRIN

- COMMON CARDIAC MEDICATION, USED IN TREATMENT OF CHF
  - FOXGLOVE
  - DIGOXIN
**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 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.

**Cardiac Effects GISSI-Prevenzione**

N=11,324 pts < 3 mo after MI on 1 Gm
- ↓ risk of death from any cause by 21%
- ↓ sudden cardiac death by 45%

**Japan EPA Lipid Intervention Study (JELIS)**

N = 18,645 with ↑ cholesterol (70% women)
- Randomized to statin or statin and pure EPA (1.8 g/d).
- At 5-years, EPA reduced major adverse CV events by 19%
There was a 6.3% median decrease in triglycerides in the simvastatin + placebo group.

**Adding LOVADA 4 g/day to Simvastatin**

- Reduced Triglycerides

  - **Baseline**
  - **End of Therapy**

  - **P=0.0001**

  - % change vs. placebo

**Post-hoc Analysis of Median Change in LDL Particle Size**

- LOVADA 4 g/day + simvastatin 40 mg/day
- Placebo + simvastatin 40 mg/day

- **P=0.0066 between groups.**

**Meta-Analysis: Predictive Value of HDL-C**

- Coronary Primary Prevention Trial (CPPT)
- Multiple Risk Factor Intervention Trial (MRFIT)
- Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCS)
- Framingham Heart Study (FHS)

**HDL-C Is a Modifier of Risk at All Levels of LDL-C**

- The Framingham Study*

**Low HDL-C Increases CVD Risk Even if LDL-C Levels Are Well-Controlled**

- Treating to New Targets (TNT) Study

- Patients With LDL-C ≤ 80 mg/dL on Atorvastatin 80 mg

- **P<0.0001 for Inverse Relationship**

*Men 50 to 70 years of age

Castelli WP, Circ J Carrot 1988;4(suppl A):5A-10A.
56 yo male distance runner
AP, CAD, CABS, + F Hx, no lipid drugs
TG = 109 mg/dl
LDLC = 121
LDL IIIa+b = 36%
HDL2b = 19%
Lp(a) = 2
Homocyst(e)line = 10/27
Apo E 4/3
Diagnosis ?
Treatment ?

Rx = Niacin 1,500 mg
TG = 109 -> 119 mg/dl
LDLC = 121 -> 109
LDL IIIa+b = 36% -> 15%
HDL2b = 19% -> 34%
Lp(a) = 2 -> 4
Conclusion ?
Minor change in lipids
Big Change in LDL & HDL subclass distribution

Case: 1734
(3/95)

Case: 1734
(7/95)
No diet is healthy without exercise!

**Lesson 3:** Move Naturally

- You lose muscle mass
- Leads to Yo-Yo dieting
- Increases cardio-vascular risk

**The Nurses’ Health Study Results**

<table>
<thead>
<tr>
<th>Exercise (quintile)</th>
<th>MET hrs/wk Median (range)</th>
<th># of CV Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8 (0 - 20)</td>
<td>178</td>
</tr>
<tr>
<td>2</td>
<td>3.2 (2.1 - 4.6)</td>
<td>153</td>
</tr>
<tr>
<td>3</td>
<td>7.7 (4.7 - 10.4)</td>
<td>124</td>
</tr>
<tr>
<td>4</td>
<td>15.4 (10.5 - 21.7)</td>
<td>101</td>
</tr>
<tr>
<td>5</td>
<td>35.4 (&gt;21.7)</td>
<td>89</td>
</tr>
</tbody>
</table>

Source: NEJM 343: 10-22

**Exercise!**

- Decreases stress
- Increases longevity
- Decreases risk of heart disease, cancer and stroke
- Decreases blood pressure
- Decreases LDL cholesterol and triglycerides
- Increases HDL
- Decreases weight
- Energizes!

**How much exercise?**

- General recommendations have been increasing over time.
- 40 minutes of aerobic exercise daily to one hour daily.
- This should be combined with muscle building activity at least three times per week.

Met ATP III criteria for primary prevention using statin therapy
- Simvastatin 40 mg/day, or
- Mediterranean diet & exercise encouraged
- Fish oil (~2 grams)
- Red Yeast Rice 2.4-3.6 Gm

Results: Lifestyle vs Simvastatin
- in LDL-C (~42.4% vs ~39.6%)
- triglycerides (~29% vs ~9.3%)
- weight (~5.5% vs ~0.4%)
- Safety: Simv: 5 pts with myalgia, LFTs
- Lifestyle: 1 pt with CK, 2 heartburn
- has promise for a subset of patients unwilling or unable to take statins
“The chief and primary cause of ... the very rapid increase of nervousness is modern civilization, which is distinguished from the ancient by these five characteristics: steampower, the periodical press, the telegraph, the sciences and the mental activity of women.”

*American Nervousness, Its Causes and Consequences*, George M. Beard, 1881

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ACPE survey 2006

- 1200 practicing physicians surveyed
- 6 in 10 doctors have considered leaving medicine
- 77% experience fatigue
- 67% experience burnout
- 33% depression & family discord
- Contributing causes:
  - Low reimbursement
  - Low autonomy
  - Patient overload
  - Lack of respect

Kaiser Family Foundation Survey

- 2,608 physicians surveyed in 2001
- 60% of physicians have had a decrease in enthusiasm, toward medical practice, in the past 5 years.
- 87% said that the overall morale of physicians has declined in the past 5 years.
- 75% said that managed care had a negative impact on their practices.

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STRESS RESPONSE

- Trophic effects
- High blood pressure
- Tachycardia
- Abnormal lipids
- Insulin resistance
- Enhanced coagulation
- Weight increase
- Parasympathetic tone
- High Renin Angiotensin

Caregivers took an average of 24% longer than well-matched controls to heal the same small, standardized wound.


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STRESS SLOWS WOUND HEALING

Caregivers took an average of 24% longer than well-matched controls to heal the same small, standardized wound.

Days to heal for each of the 11 students; no student healed as rapidly during exams, with the average student taking 40% (3 days) longer.

Replication with caregivers published by Vedhara et al. in *Lancet*, 1999

- 25% increase in myocardial infarction admissions in London on the day of the match when England lost to Argentina in a penalty shootout during the 1990 World Cup. *BMJ*, 2002;325:1438-1442.
Anger and MI

- 1623 heart patients tracked
- “What happened the two hours before your MI?”
- Anger increased risk of MI by 230%
  - Mittleman et al., Circulation, 1995, vol. 92

Stress Mastery

- Change your environment
- Change how you react and perceive your environment

Social Support As An Intervention

Lesson 5 & 6: Belong, Family

Depression

- 218 patients followed for 18 months post MI
- 75% of the post MI deaths are related to depression in the next 6 months
- This was independent of other risk factors
  - Frasure-Smith et al., JAMA 1993, vol. 91
Social Support, Depression And Cardiac Death Rates

- This effect was negated when people felt socially supported
  - Frasure-Smith et al, Circulation, 2000 vol. 101

Community and disease risk: Roseto, PA

- Lower incidence of MI than surrounding communities before the 1970’s
- Similar diets, weights, smoking behaviors and diabetes prevalence to surrounding communities

Predictors of MI in Roseto, PA

50 year prevalence shift
- Before the 1970’s:
  - Three generation households were prevalent
  - High degree of religiosity and traditional values
- After the 1970’s:
  - Break up of multigenerational households
  - Decreasing church attendance
  - Increasing mobility
  - MI prevalence equal to surrounding communities


Lesson 7: Right Tribe

Spirituality in Medicine

- 90% of people believe in a higher being
- 94% regard their spiritual and physical health as equally important
- 96% of FP believe that spiritual well-being is a factor in health


Religion and Heart Disease

- Religious attenders:
  - Lower systolic and diastolic BP
  - Greater compliance with medication
  - Exercise more
  - Eat healthier
  - Quit smoking more readily

Lesson 8: Plan de Vida

- A study of 700 older adults
- Those who gave love and support to others had significantly fewer health issues

Depner, CE and Ingersoll-Dayton, Psychology and Aging, 1988, 3:348-57

Helpers High

- Half of helpers report a high feeling
- 43% felt stronger and more energetic
- 28% felt warm
- 22% calm and less depressed
- 21% greater feeling of self worth
- 13% fewer aches and pains

Luks Psychology Today 1988

AA 12 Step Program

- 12 step program
- Likelihood of relapse was twice as high for non-helpers than helpers; 40% vs. 22%

Pagano, et al J of studies on Alcohol, 2004

Conclusion

- The causes of cardiovascular disease are multifactorial
- Diet and exercise is associated with a 50% reduction in morbidity and mortality
- Psychosocial risk should be considered with the same rigor as more traditional risk factors
- A multi-disciplinary team of health providers is needed
- Listen to your 95-year-old patients!