Diabetes and the Cardiovascular Connection

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Today’s Agenda

1. What is Cardiovascular Disease?
   *Coronary Artery Disease and Heart Attack*

2. What is the BIG DEAL?

3. Risk Factors for Cardiovascular Disease

4. The Guidelines/Risk Factor Management
   - *Glucose Control-How Low Should We Go?*
   - *Risk Factor Treatment Strategies*

5. Additional Risk Factors to Consider
Ms. J

56 year old woman

- Diabetes
- High Blood Pressure
- High Cholesterol
- Depression

Presents with throat tightness at 1:30 pm

“You have a cold, wait here”

In Radiology at 8:00 pm . . .

The Resuscitation Room . . .
The Rest of the Story . . .

- Status-post a successful intervention of the right coronary artery.
- Moderately reduced ventricular function with chronic congestive heart failure
1. What is Cardiovascular Disease?
Percentage Breakdown of Deaths from Cardiovascular Diseases

- Coronary Heart Disease: 54%
- Stroke: 18%
- Congestive Heart Failure: 6%
- High Blood Pressure: 5%
- Diseases of the Arteries: 4%
- Rheumatic Fever/Rheumatic Heart Disease: 4%
- Congenital Cardiovascular Defects: 0.4%
- Other: 13%

Other 13%

Every Woman, Tell a Woman.
Fatty Streaks

85% of people ages 21-39 years have fatty streaks.
Women are less likely to have calcified, mixed composition lesions.
Ischemic Heart Disease
What is the BIG DEAL?
Coronary Artery Disease 2006: A Disease of the Arteries of the Heart

More than 6.9 million Americans are affected each year

- 785,000 new heart attacks
- 470,000 recurrent attacks
- 631,636+ deaths
Coronary Artery Disease:

- #1 cause of death in women and men in America and in most industrialized nations

Stroke:

- #3 cause of death of Americans
Leading Causes of Death for All Males and Females
United States: 2002

Source: CDC/NCHS
Percentage of All Deaths Caused by Heart Disease in 2004

<table>
<thead>
<tr>
<th>Race/Ethnic Group</th>
<th>% of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>25.8</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>19.8</td>
</tr>
<tr>
<td>Asians/Pacific Islander</td>
<td>24.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22.7</td>
</tr>
<tr>
<td>White</td>
<td>27.5</td>
</tr>
<tr>
<td>All</td>
<td>27.2</td>
</tr>
</tbody>
</table>
CVD Disease Mortality Trends for Males and Females

(United States: 1979-2006).
Source: NCHS and NHLBI.
3. Risk Factors
Risk Factors

Non-modifiable versus Modifiable
#1 Risk Factor: Family History of Premature Heart Disease

Father with Heart Disease < age 55

Mother with Heart Disease < age 65
Non-modifiable Risk Factors

Sex
Non-modifiable Risk Factors

Age
Menopause

- Estrogen
- HDL

Weight & Blood Pressure

LDL & Triglycerides
Modifiable Risk Factors

- Diabetes/Glucose Intolerance*
- Tobacco
- High Blood Pressure*
- Dyslipidemia*
- Obesity*
- Obstructive Sleep Apnea*
- Lack of Exercise*
- Drug Use
- Dental Disease
- Newer Modifiable Risks
  - Hostility/Anger
  - Stress*
  - Anxiety/Depression
The Diabetes Explosion
Number of Actual Cases

1958 '61 '64 '67 '70 '73 '76 '79 '82 '85 '88 '91 1994

Millions

The New York Times - September 7, 1999
Diabetes is a Coronary Heart Disease Equivalent
What’s the Risk of Heart Disease for People with Diabetes?

For Men: 2-3 times greater

For Women: 4-6 times greater
Mr. B.
24 year old Hispanic male

Cardiac Risk Factors: None

Symptoms: Intermittent exertional throat tightness

Presentation #3 . . .
The Evaluation

ECG: Normal

CXR: Normal

Laboratories:
- Glucose 240
- Sodium 132
- Potassium 5.2
- Creatinine 1.6
- Troponin 8.3
Angiography
The Rest of the Story . . .

- Type II Diabetes
- Dyslipidemia
- Cardiac Surgery Consultation
- Cardiac Rehabilitation
- Aggressive management of risk factors
Physiologic Effects of Hyperglycemia

Metabolic stress response

Stress hormones and peptides

Glucose
↓Insulin

↑Glucose
↓Insulin

↑FFA
↑Ketones
↑Lactate

Cell injury/apoptosis
Inflammation/tissue damage
Altered tissue/wound repair
Acidosis
Infarction/ischemia

Prolonged hospital stay
Disability

↑Platelet aggregation
↓tPA activity
↑PAI levels

↑Reactive Oxygen Species
↑Transcriptional function
↑Secondary mediators

Immune dysfunction
Infection dissemination

Deedwania, P. et al. Circulation
2008:117.1610-19
Cardiovascular Effects of Hyperglycemia

Deranged Metabolism
- ↑Serum-free fatty acids
- ↑Insulin secretion
- ↓Glycolysis
- ↓Glucose Oxidation

Impaired Perfusion
- ↓Endothelial Function
- ↑No-reflow phenomenon

Impaired LV Function
- ↓Ischemic preconditioning
- ↑Left ventricular remodeling

Prothrombic
- ↑Platelet aggregation
- ↓Fibrinolysis
- ↑Clotting Factor

Inflammation
- ↑Cytokines/chemokines
- ↑C-reactive Proteins

Insulin’s Effects

Anti-inflammatory
- ↓NF-κB
- ↓MCP-1
- ↓ICAM-1
- ↓CRP

Antithrombotic
- ↓TF
- ↓PAI-1

Anti-oxidative
- ↓ROS
- ↓NE-FFA

Insulin Effects

Vasodilatory + Platelet inhibitory
- ↑NO release
- ↑cAMP
- ↑eNOS

Antiapoptotic
Glucose lowering

Characteristics of Metabolic Risk

• Central Obesity
• Insulin Resistance
• Dysproteinemia
• Hypertension

• American Diabetic Association and the American College of Cardiology Foundation established lipid guidelines for patients with metabolic syndrome, Spring 2008
Acanthosis Nigricans and Skin Tags

Clinical marker of hyperinsulinism and metabolic syndrome

Skin tags are not often seen before the age of 40 years

The severity of skin darkening and number of skin tags parallel the degree of insulin resistance

Weight reduction and improvement in IR can result in partial resolution of acanthosis nigricans
Even in the absence of CVD and diabetes, individuals with metabolic syndrome have a significantly higher risk of CAD and all cause mortality. Hu, et al 2004
Prevalence of Metabolic Syndrome

![Graph showing the prevalence of NCEP ATP III Metabolic Syndrome among subjects in the NHANES III Survey, by age.](image)

Developing Type 2 Diabetes

~57 million people in the US have prediabetes

We can delay or prevent diabetes with diet and exercise
## Contribution of Diabetes to CHD

**Strong Heart Study**

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>6.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Prevalence</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td><em>Attributable risk</em></td>
<td>76%</td>
<td>51%</td>
</tr>
</tbody>
</table>

*Diabetes is the engine driving the increase in CVD*
Mr. H.
65 year old male

Cardiac Risk Factors:
• Dyslipidemia
• Hypertension

Symptoms:
• Marked diaphoresis following an evening meal
Mr. H., cont.

ECG:
Anterior Myocardial Infarction

Laboratories:
Troponin 3.2
Creatinine 1.3
Non-fasting Glucose 176
Hematocrit 39
The Widow Maker
The Rest of the Story . . .

- Multi-vessel coronary artery disease
- Status-post staged percutaneous interventions
- Lipid management
- Blood pressure management
- Persistently elevated blood sugars
Patients presenting with chest pain and an acute coronary syndrome have a 70% chance of having diabetes or pre-diabetes.
Who Should Be Screened?

- Those $\geq 45$ years of age (particularly if BMI $> 25$)
  - Repeat in 3 years if normal

- Screen earlier and more often if BMI $\geq 25$ plus:
  - Physically inactive
  - First degree relative with Type 2 DM
  - High risk ethnic group
  - Hypertensive $\geq 140/90$ mmHg
  - HDL $< 35$ and/or Triglycerides $> 250$
  - History of gestational DM or baby $\geq 9$ lbs
  - History of PCOS
  - Previous IGT or IFG
  - History of vascular disease

Diabetes Care Jan 2010
Prediabetes

• Impaired glucose tolerance (IGT)
  – Plasma glucose $\geq$ 140 mg/dl but < 200 mg/dl after 75 gram glucose load
  – Better predictor of individuals who will go on to DM
• Impaired fasting glucose (IFG)
  – Fasting plasma glucose concentration $\geq$ 100 mg/dl but < 126 mg/dl
• Hemoglobin A1c $\geq$ 5.7%

Rate of progression to DM is ~25% over 3-5 years for either IGT or IFG
Progression 8-10% per year in recent prevention trials
Diagnosing Diabetes in 2010

- HbA1c ≥ 6.5%
- Fasting blood glucose of 126 mg/dl or higher
- A 75 gram glucose tolerance test with a two hour glucose value ≥ 200 mg/dl
- Should have two positive tests to make the diagnosis

Diabetes Care 2010;33(suppl1)
UKPDS Myocardial Infarction (cumulative)

fatal or non fatal myocardial infarction, sudden death of 3867 patients (15%)

Risk reduction 16%

% of patients with an event vs Years from randomization

Conventional

Intensive

Risk reduction 16%

UKPDS HbA$_{1c}$ trend

- **Conventional**
- **Intensive**

Cross-sectional, median values
HbA$_{1c}$ (%)

- 6.2% upper limit of normal range

Years from randomization
How Low Should We Go?

Reprinted from JAMA 2008;299(12):1413-1415
## ACCORD, ADVANCE and VADT Study Design

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Endpoints</strong></td>
<td>CV death, Non-fatal MI/Stroke</td>
<td>CV death, Non-fatal MI/Stroke, macrovasc event</td>
<td>CV death, Non-fatal MI/Stroke, CHF macrovasc event</td>
</tr>
<tr>
<td><strong>Study</strong></td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>Glucose Intensive vs Standard Arm 2x2 BP control +/- fenofibrate v placebo</td>
<td>Glucose Intensive vs Standard Arm 2x2 Perindopril +indapamide v placebo</td>
<td>Glucose Intensive vs Standard Arm 2x1 All received BP and Lipid Rx</td>
</tr>
</tbody>
</table>

VADT Study Results ADA Scientific Session San Francisco, 2008.  
In Press, Diabetes Obesity and Metabolism, 2008.
## Therapeutic Approach: ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meds (Inten v Std)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>95 v 87 %</td>
<td>74 v 67 %</td>
<td>75 v 71%</td>
</tr>
<tr>
<td>TZD (Rosi)</td>
<td>91 v 58 %</td>
<td>17 v 11%</td>
<td>85 v 78%</td>
</tr>
<tr>
<td>Oral Hypoglycemic</td>
<td>87 v 74 %</td>
<td>94 v 84 %</td>
<td>55 v 45%</td>
</tr>
<tr>
<td>Insulin</td>
<td>73 v 58 %</td>
<td>41 v 24 %</td>
<td>90 v 74%</td>
</tr>
<tr>
<td>Exenatide</td>
<td>12 v 4 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Follow-up intensive</td>
<td>Q mo x 4, then q 2 mo</td>
<td>Q mo x 4, then Q 3 mo</td>
<td>-</td>
</tr>
<tr>
<td>group</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VADT Study Results ADA Scientific Session San Francisco, 2008
# Outcomes: Summary of ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th></th>
<th>ACCORD*</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>6.4 vs. 7.5 †</td>
<td>6.4 vs. 7.0 †</td>
<td>6.9 vs. 8.4 †</td>
</tr>
<tr>
<td>(Intensive vs. Std)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI (%)</td>
<td>3.6 vs 4.6% †</td>
<td>2.7 vs. 2.8</td>
<td>6.3 vs. 6.1</td>
</tr>
<tr>
<td>(Intensive vs. Std)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death (%)</td>
<td>2.6 vs. 1.8 †</td>
<td>4.5 vs. 5.2</td>
<td>2.1 vs. 1.7</td>
</tr>
<tr>
<td>(Intensive vs. Std)</td>
<td>(1.35 Hazard Ratio)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvascular</td>
<td>-</td>
<td>nephropathy ↓ 21%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>retinopathy ↓ 5% NS</td>
<td></td>
</tr>
<tr>
<td>Take home</td>
<td>↓ risk MIs, but ↑ risk death in intensive arm</td>
<td>Glucose control has no impact on CV events, but ↓ Microvascular risk</td>
<td>Glucose control has no impact on CV events</td>
</tr>
</tbody>
</table>

*ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial halted intensive glucose group (2/6/08)
† significant difference between intensive and standard group

VADT Study Results ADA Scientific Session San Francisco, 2008
In Press, Diabetes Obesity and Metabolism, 2008.
Hazard Ratios for the Primary Outcome and Death from Any Cause in Pre-specified Subgroups: ACCORD Study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10,251</td>
<td>460</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6,643</td>
<td>220</td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Yes</td>
<td>3,608</td>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,952</td>
<td>132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6,299</td>
<td>328</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>6,779</td>
<td>212</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>3,472</td>
<td>248</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8.0%</td>
<td>4,868</td>
<td>204</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;8.0%</td>
<td>5,360</td>
<td>256</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>3,647</td>
<td>131</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>White</td>
<td>6,604</td>
<td>329</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prior CVD

Age >65

A1c >8.1
Accord, Advance, and VADT Lessons Learned

• Intensive glucose control does not reduce CVD mortality in T2DM, and *may* increase risk, especially in patients with pre-existing coronary heart disease

• Aggressive A1c targets (<6.5%) were associated with a 3-fold increased risk hypoglycemia

• No excess CVD mortality was seen with Rosiglitazone
Accord, Advance, and VADT
Lessons Learned

• Intensive control was associated with reduced risk for nephropathy in ADVANCE

• To reach and maintain A1c targets of <6.5, required frequent adjustments of multiple anti-diabetic medications

• Aggressive Targets (<6.5) are probably reasonable for healthy patients to reduce risk micro-vascular complications
ADA Consensus Statement on Medical Management of Hyperglycemia in Type 2 Diabetes

• Achieve and maintain near normoglycemia, A1c <7.0

• Initiate therapy with lifestyle modification and Metformin

• Rapid addition of medications, and transition to new regimens when targets are not achieved

• Early addition of insulin therapy in patients who do not meet target goals
Thiazolidinediones (TZDs)

- TZDs have been under intense scrutiny in recent years after rosiglitazone was linked to increased CV morbidity and mortality
- ACC/AHA insufficient evidence to support the use of pioglitazone over rosiglitazone, as both drugs increase the risk of heart failure
  - Neither drug should be initiated in patients with class III/IV heart failure
- These drugs should not be used with the expectation of benefit in ischemic heart disease events  
  
  ACCORD, ADVANCE, VADT demonstrated no increased mortality with the use of rosiglitazone
- FDA planning public meeting in July 2010 to present all heart-related safety data with updated assessment of risks and benefits of rosiglitazone and treatment of T2DM
What About Blood Pressure?
# Blood Pressure Classification

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg/DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 and &lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139 or 80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159 or 90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160 or &gt;100</td>
</tr>
</tbody>
</table>
**Benefits of Lowering Blood Pressure**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Average Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Incidence</td>
<td>35-40%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>20-25%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>50%</td>
</tr>
</tbody>
</table>
## Lifestyle Modification

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP Reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5-20 mmHg/10Kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2-4 mmHg</td>
</tr>
<tr>
<td>Compelling Indication</td>
<td>Initial Therapy Options</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>High CAD Risk</td>
<td>Thiazides, BB, ACEI, CCB</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Thiazides, BB, ACEI, ARB, CCB</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>ACEI, ARB</td>
</tr>
</tbody>
</table>
Hypertension Management in Diabetics in 2010
• 4733 patients, randomized, non-blinded, to intensive therapy (SBP < 120mmHg) or standard therapy (SBP < 140mmHg)

No significant difference in the primary end point or pre-specified secondary end points except in the cases of stroke

• Primary endpoint: nonfatal myocardial infarction, nonfatal stroke, or CV death

• Secondary end point: primary outcome plus revascularization or nonfatal CHF; major coronary disease events; and fatal or nonfatal CHF

• Mean follow-up of 4.7 years
• 40% reduction in stroke for 5-10 mmHg reduction in blood pressure

• Patients in the intensive-therapy group were more likely to suffer adverse events due to antihypertensive therapy 3.3% vs 1.3% (p<0.001)
Blood Pressure Recommendations for Type II Diabetics

• “Optimal blood pressure target in patients with diabetes unresolved” Nilsson PM (editorial) NEJM 2010 DOI:1056/NEJMe1002498

• Avoid aggressive blood pressure control

• Goal SBP < 140 mmHg
Ms. B.
46 year old woman
- PCOS

Symptoms:
One week history of intermittent substernal and left-sided chest pressure and nausea

Her symptoms wax and wane and have been present both at rest and with exertion.
Ms. B’s
Coronary Angiogram

90% Blocked with Plaque
The Rest of the Story . . .

- Status post single vessel coronary artery bypass grafting
- Subsequently diagnosed with high cholesterol and insulin resistance
Hyperlipidemia

The “GOOD”  (HDL)

The “BAD”  (LDL)

The “UGLY”  (Triglycerides)
High Density Lipoprotein: HDL = Good Cholesterol

Low HDL is BAD
HDL vs LDL as a Predictor of Coronary Heart Disease

- The Framingham Heart Study showed that the lower the level of HDL-C, the greater the risk of a coronary event, regardless of LDL-C level.

- In fact, a person with a “desirable” LDL-C of 100 mg/dL but a low HDL-C of 25 mg/dL has the same risk for an event as a patient with an LDL-C of 220 mg/dL who has an HDL-C of 45 mg/dL\(^1,2\)

- As many as two-thirds of patients with CHD have low levels of HDL-C (≤40 mg/dL)\(^3\)

---

Variable TG and PL content: Oxidative susceptibility

Large VLDL → Remnant → Apo B
Muscle/Fat tissue → HL → IDL → Small LDLs
Liver HL → Small VLDL → LPL

Removal By Liver

Chol return from HDL2 to LDL

Antioxidant Paraoxonase

LDL pattern B: LDL more susceptible to oxidative damage *

Remnant

HDL3

IVb
IVA
IIIb
IIIa
Large LDLs

Small LDLs: Rapid entry/Oxidation

Muscle/Fat tissue

HDL2b

Plaque

CETP

HDL3

endothelial cells
Management of HDL

- **Lifestyle intervention**
  - Diet
  - Exercise
  - Tobacco cessation

Low HDL is a powerful predictor of risk for coronary heart disease; raising HDL reduces coronary heart disease risk

- **Drug options**
  - Niacin (+10-30%)
  - Fibrates (+5-25%)
  - Statins (+3-12%)
Low Density Lipoprotein: LDL = Bad Cholesterol

- Better predictor of coronary artery disease in men than in women
- Plateaus in men after age 50, continues to rise in women until at least age 65
Triglycerides=Ugly

- Underestimation of the association between TG and disease in a multivariate analysis

- Individual genetic susceptibility may play an important role in the relationship between plasma TG levels and CVD

- 76% increase CVD risk in women
- 31% increased CVD risk in men
  (Associated with 1 mmol/L increase in TG levels)
Lipids And Lipoproteins in Patients with Insulin Resistance and T2DM

- Clustering of interrelated plasma lipid and lipoprotein abnormalities
  - Reduced HDL$_{2b}$
  - Predominance of small dense LDL particles
  - Elevated triglyceride levels

- Increased hepatic secretion of TG-rich VLDL and impaired clearance of VLDL is central in the pathophysiology of “metabolic” dyslipidemia
Components Of The VAP Profile

• Non-HDL
  – Difference between total cholesterol and HDL-C
  – Includes all cholesterol present in lipoprotein particles considered atherogenic
    • LDL
    • Lipoprotein(a)
    • IDL
    • VLDL
  – May be a better tool for risk assessment than LDL-C
  – Secondary target in patients with high TG: Goal non-HDL is 30 mg/dl higher that that for LDL-C
Components of The VAP Profile

- **LDL Particle Size**
  - A (desirable)
  - A/B
  - B

- **HDL subunits**
  - HDL-2 is cardioprotective

- **Apo B-100**
Lipoprotein Guidelines in Patients with Metabolic Risk (MR)

- Patients with known cardiovascular disease or diabetes plus one or more additional major CV risk factor
  - LDL < 70 mg/dl
  - Non-HDL < 100 mg/dl
  - apo-B < 80 mg/dl
  - TG < 100 mg/dl
  - HDL > 55 in a woman; > 45 in a man
Lipoprotein Guidelines in Patients with Metabolic Risk (MR)

- Patients without diabetes, but with two or more additional major CV risk factors
- Diabetics without other major CV risk factors

- LDL < 100 mg/dl
- Non-HDL < 130 mg/dl
- apo-B < 90 mg/dl
- TG < 150 mg/dl
- HDL > 55 for a woman; > 45 for a man
# The VAP Profile

<table>
<thead>
<tr>
<th>TEST NAME</th>
<th>RESULT</th>
<th>UNITS</th>
<th>FLAGS</th>
<th>REF RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAP CHOLESTEROL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIRECTLY MEASURED LIPID PROFILE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total LDL-Cholesterol-Direct</td>
<td>237</td>
<td>&lt;130 mg/dL</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Total HDL-Cholesterol-Direct</td>
<td>58</td>
<td>&gt;=40 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total VLDL-Cholesterol-Direct</td>
<td>23</td>
<td>&lt;30 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sum Total Cholesterol</td>
<td>317</td>
<td>&lt;200 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Triglycerides-Direct</td>
<td>112</td>
<td>&lt;150 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Total Non-HDL Cholesterol (LDL+VLDL)</td>
<td>260</td>
<td>&lt;160 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Total apoB100-Calc.</td>
<td>160</td>
<td>&lt;109 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>FOR CLINICAL JUDGMENT IN SETTING LDL-C GOAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a) Cholesterol</td>
<td>19.0</td>
<td>&lt;10 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>IDL Cholesterol</td>
<td>22</td>
<td>&lt;20 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>LDL-R(Real)-C</td>
<td>197</td>
<td>&lt;100 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sum Total LDL-C</td>
<td>387</td>
<td>&lt;130 mg/dL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Real-LDL Size Pattern</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remnant Lipoproteins (IDL+VLDL3)</td>
<td>25</td>
<td>&lt;30 mg/dL</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

**CONSIDER INSULIN RESISTANCE/METABOLIC SYNDROME**

**Constellation of Lipid Risk Factors**
- (small dense LDL, elevated TG, low HDL)

**SUB-CLASS INFORMATION**
- HDL-2
  - (Large, Buoyant; most protective) | 17 | >15 mg/dL | + |
- HDL-3
  - (Small, Dense; least protective) | 41 | >25 mg/dL | + |
- VLDL-3 (Small Remnant) | 13 | <10 mg/dL | + |

* **REPORT FAXED 02/11/08**

**Test performed at:** Atherosach
201 London Parkway
Birmingham, AL 35211
Although behavioral interventions such as diet and exercise can improve diabetic dyslipidemia, most diabetic patients will need pharmacological therapy to reach treatment goals.
Statin Therapy in Diabetics?

- 18,686 patients with diabetes
- Meta-analysis of 14 randomized trials of statins
- Statins should be considered for all diabetic individuals who are at sufficiently high risk of vascular events
Niacin Therapy

• Niacin improves all lipoprotein abnormalities
  (Ideal for treating a wide variety of lipid disorders)
  – Metabolic syndrome
  – Diabetes
  – Isolated low HDL
  – Hypertriglyceridemia

• Converts small LDL particles into more buoyant, less atherogenic cholesterol
Case: 1734 (7/95) Courtesy of Dr. M. Guarneri

Rx = Niacin 1,500 mg
TG = 109 -> 119 mg/dl
LDLC = 121 -> 109
LDL IIla+b = 36% -> 15%
HDLC = 42 -> 45
HDL2b = 19% -> 34%
Lp(a) = 2 -> 4

Conclusion:
Minor change in lipids
Major Change in LDL & HDL subclass distribution
Niacin Therapy in Diabetes

• Major drug for treatment of diabetic dyslipidemias

• Is effective for separately treating diabetic dyslipidemia associated with abnormal LDL size, HDL$_2$, and Lp(a) independent of hemoglobin levels

• Must be used with modern and aggressive oral hypoglycemic agents or insulin,
Niacin + Simvastatin Therapy in Diabetes

- Effective, safe and well tolerated
- Slowed the progression of atherosclerosis among individuals with known CAD and moderately low HDL
ACCORD Lipid Study

- 5518 patients (2765 fenofibrate plus simavastatin/2753 placebo plus simvastatin)

- Men seemed to benefit from fenofibrate therapy, with trend toward harm in woman

- The combination of fenofibrate and simvastatin did not reduce the rate of fatal CV events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone

- Patients with higher triglycerides and lower HDL cholesterol levels benefited from fenofibrate therapy in addition to simvastatin

NEJM 2010;DOI:10.1056/NEJMoa1001282
4. Additional Risk Factors
Mr. M

- 53 y/o bank executive with T2DM, and dyslipidemia presents at 2:30 pm following a fainting spell during a post lunch meeting

- ECG reveals a lateral myocardial infarction

- Laboratories: Troponin 6.2
  Cr 1.1
  Platelets 357
  Hct 42

- Outpatient Labs: HgA1c 6.1%, LDL 86, HDL48, TG 158
Blood Cholesterol is NOT the Best Indicator of Heart Disease Risk

High blood cholesterol is an important CAD risk factor

• However...
  80% of people who develop CAD have the same blood cholesterol values as those who do not develop CAD

Coronary Heart Disease Risk and Total Serum Cholesterol in Framingham
Atherosclerosis Is an Inflammatory Disease

Inflammation is a Risk Factor for MI

P-Trend < 0.001

Relative Risk of MI in Healthy Men

Quartile of C-Reactive Protein (range, mg/dL)

0 1 2 3 4
0 <0.055 0.056–0.114 0.115–0.21 ≤0.211

Adapted from N Engl J Med 1997;336:973-979.
## Nutrition and Inflammation

<table>
<thead>
<tr>
<th>Foods that increase inflammation</th>
<th>Foods that decrease inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red meat, eggs</td>
<td>Cold-water fish</td>
</tr>
<tr>
<td>Sugar</td>
<td>Spices and herbs turmeric, rosemary, ginger, Hot peppers</td>
</tr>
<tr>
<td>Coffee, alcohol</td>
<td>Green tea</td>
</tr>
<tr>
<td>High-Glycemic Foods</td>
<td>Low-Glycemic Foods</td>
</tr>
</tbody>
</table>
Aspirin Therapy in Diabetes?
Aspirin Therapy in Diabetes

- Platelets in patients with diabetes are often hypersensitive to platelet aggregating agents in vitro.
- The major mechanism is increased production of thromboxane.
- Excess thromboxane release is seen in T2 diabetics with CVD.
- Aspirin blocks thromboxane synthesis by acetylatining platelet cycloxygenase.
Recommendations for Aspirin Therapy in Diabetic Patients

- Secondary prevention in diabetic patients with h/o myocardial infarction, vascular bypass procedure, stroke or tia, peripheral vascular disease, claudication and/or angina (A)

- Primary prevention in T1 and T2 diabetics at increased CV risk (>40 years, Fhx of CVD, HTN, smoking, dyslipidemia, albuminuria) (A) (C)

- Contraindications: aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease (E)

- Aspirin therapy should not be recommended for patients under the age of 21 years because of the increased risk of Reye’s syndrome associated with aspirin use in this population. People under the age of 30 have generally not been studied. (E)
Aspirin and ACE Inhibitor Therapy

In patients with CVD, the benefits of ACE inhibitor therapy are reduced when used in conjunction with aspirin therapy.
In Cases of Aspirin Allergy . . .

- Clopidogrel is a reasonable alternative
  - In the CAPRIE trial, clopidogrel (75 mg) was slightly more effective than aspirin (325 mg) in reducing the combined risk of stroke, myocardial infarction, or vascular death in diabetic and non-diabetic subjects

Mrs. S
73 year old grumpy, obese woman
- High Blood Pressure
- Diabetes
- Atrial Fibrillation

Presents for further evaluation of palpitations that often awaken her from sleep
At night . . .
The Rest of the Story . . .

• Diagnosis and treatment of sleep apnea

  Improved energy
  Improved blood pressure
  Improved blood sugar control
  Reduced crabbiness
  Reduction in her episodes of arrhythmia
Obstructive Sleep Apnea

• Cardiovascular Conditions Associated with Obstructive Sleep Apnea
  Hypertension
  Cardiac Arrhythmias
    Bradycardia
      Sinus Bradycardia
      Atrioventricular Block
    Tachydysrhythmia
      Supraventricular Tachycardia
      Atrial Fibrillation
      Ventricular Tachycardia
  Left Ventricular Systolic Dysfunction
  Left Ventricular Diastolic Dysfunction
  Congestive Heart Failure
  Stroke
  Coronary Artery Disease
  Pulmonary Hypertension
Vascular Inflammation in Obesity and Sleep Apnea

• Untreated OSA, rather than obesity is a major determinant of vascular endothelial dysfunction, inflammation, and elevated oxidative stress in obese patients

• Cardiometabolic effects of OSA include:

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Increased hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heightened sympathetic tone</td>
<td>Reactive platelets</td>
</tr>
<tr>
<td>Dysglycemia</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Increased cortisol, leptin</td>
<td>Increased growth hormone</td>
</tr>
</tbody>
</table>
Restorative Sleep Is A Must !
Obesity is a U.S. Epidemic

• Obesity is strongly associated with increased risk of heart attack and death from heart disease

• Nearly 33% of children are overweight

• 66% of adults are overweight
Childhood Obesity

- It is easier to prevent obesity in childhood than to cure it in adulthood.

- A 6 year old obese child has a 25% chance of being an obese adult.

- A 12 year old obese child has a 75% chance of being an obese adult.
Young Ms. J

A happy sedentary young girl who likes to eat

• By age 8:
  – Weight 165 lbs.
  – Diagnosed with Type II, “adult onset” diabetes

• By age 18:
  – Weight 412 lbs.
  – Sought treatment for her obesity
How to Calculate Body Mass Index (BMI)

\[ \text{BMI} = \frac{\text{Weight}}{\text{Height}^2} \times 703 \]

**Example:**
- **Weight:** 185 lbs.
- **Height:** 64 in. (5’4”)

\[ 185 \div (64 \times 64 = 4096) = .045 \times 703 = 31.6 \text{ BMI} \]

- **Normal BMI:** 18.5-24.9
- **Overweight:** 25.0-29.9
- **Obese:** \( \geq 30.0 \)
- **Morbidly Obese:** \( \geq 50 \)
Obesity is Increasing Rapidly Throughout the United States

Obesity Prevalence in 1993
15-19% in 12 states
20+% in 0 states

Centers for Disease Control and Prevention, 2003
Obesity is *Increasing* Rapidly Throughout the United States

**Obesity Prevalence in 1993**
- 15-19% in 12 states
- 20+% in 0 states

**Obesity Prevalence by 2003**
- 15-19% in 15 states
- 20-24% in 31 states
- 25+% in 4 states

Centers for Disease Control and Prevention, 2003
Obesity Trends* Among U.S. Adults
BRFSS, 2006

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
WHAT REALLY MAKES YOU FAT?

The latest science on how your body handles CARBS vs. FATS
Fat is Down, Calories are Up

% OF TOTAL DAILY CALORIES FROM FAT
Today: 34%
1960s: 42%

Today calorie consumption is dramatically higher (more simple carbohydrates, fewer fresh fruits and vegetables)

Eckle, RH & Krauss, RM; Circulation. 1998;97:2099-2100
The Size of Individual Servings has Increased Significantly

1894 Cola Drink

6.5 oz.
79 calories

Today
Cola Drink

20 oz.
250 calories
The Size of Individual Servings has Increased Significantly

1957
Popcorn
3 cups
170 calories

Today
Popcorn
16 cups
900 calories
Obesity Treatment

• Diet and exercise critical

• Yoga

• Counseling/behavioral modification

• Medications

• Bariatric surgery
A Physically Inactive Lifestyle Doubles The Risk Of Heart Disease

Inactivity causes:

- 12% of total deaths in the U.S.
- 250,000 deaths each year
Steven Blair showed that modest exercise decreased heart disease deaths by 50% in both men and women.

Journal of The American Medical Assn. 1989
EXERCISE

Some motivation required.
Exercise Truths

- Fit obese men had lower death rates than unfit lean men!

- Sedentary women who became active in mid life, or later, had a lower incidence of coronary events
  - Nurses’ Health Study

- Healthy women benefit from light to moderate exercise; benefit is based upon duration of activity, not pace
  - Women’s’ Health Study
How Much Exercise?

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

YIKES!
75-90% of all visits to healthcare providers result from stress-related disorders. American Institute of Stress.
Stress Response Pathway

Stimuli

Hypothalamus

Anterior Pituitary

Adrenal Cortex

Cortisol

Blood sugar

Adrenal Medulla

Epinephrine

NorEpinephrine

HTN, High Chol

Sympathetic Post-Ganglionic Neurons

NorEpinephrine

Arrhythmia

HPHPA Axis

SAM Axis
How Does Stress Contribute to Heart Disease?

<table>
<thead>
<tr>
<th>Stress Makes Other Factors Worse</th>
<th>Effects of Chronic Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure Increases</td>
<td>Can cause persistently elevated levels of stress hormones</td>
</tr>
<tr>
<td>Cholesterol Increases</td>
<td>• Adrenaline</td>
</tr>
<tr>
<td>Tendency to Overeat</td>
<td>• Cortisol</td>
</tr>
<tr>
<td>Exercise Less</td>
<td>Changes the way blood clots, increasing risk of heart attack</td>
</tr>
<tr>
<td>Smoke, Drink, Take Drugs</td>
<td></td>
</tr>
</tbody>
</table>
Stress Management and Exercise

• A study examining the effects of exercise or stress management training on “mental stress tests”

Stress management training reduced the risk of cardiac events by 74% and lead to decreased ischemia on repeat testing

Exercise training decreased risk, but was not statistically significant

What Should YOU Do?
Be Sure to Stop and Smell the Roses
Promotion of Health

“Health is not merely the absence of disease, but the presence of a state of well being.”

- Nutrition
- Movement
- Restorative Sleep
- Stress Reduction
Prevention Is the Key

• Be Proactive
• Identify and Treat Patient’s Risk Factors
• Educate
• Encourage Patients To Talk With Family and Friends
• Get Moving

Every Woman, Tell A Woman.
Thank You