Aggressive Risk Factor Management in the Prevention Of Coronary Artery Disease

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- None

Coronary disease.....2009

- In 2005, CHD caused 1 in 5 deaths in the United States
  - Single largest killer of American males and females
- About every 25 seconds, an American will suffer a coronary event
  - In the US, one person dies every 1 minute from CHD
- In 2009, estimated direct and indirect costs of CHD are 165.4 billion dollars.

Heart Disease and Stroke Facts – 2009 Update, American Heart Association, Dallas Texas.

CAD prevention.....

- The process of retarding the natural progression of vascular obstruction that leads to myocardial ischemia, injury or infarction.
  - Anticipating
  - Thwarting
  - Forethought of cause
- What are the goals of prevention?

Endothelium: The root cause?

- Injury to the endothelium appears to be the key event in:
  - The origin
  - The progression
  - The clinical manifestation of atherosclerotic plaques
- Endothelial dysfunction increases the likelihood for the presence of other risk factors


Risk factors for the development of endothelial dysfunction

- Catalysts of endothelial dysfunction
  - Aging
  - Insulin resistance
  - Impaired glucose tolerance/Impaired fasting glucose
  - Hypertension
  - Dyslipidemia
  - Tobacco use
  - Sedentary lifestyle
  - Diet

Heart Disease and Stroke Facts – 2009 Update, American Heart Association, Dallas Texas.
Case study

Barbara: Presents to her primary care provider to assess her risk for Coronary Artery Disease after attending a "health fair".

Her summary evaluation suggested she visit her primary care provider for a comprehensive risk evaluation.

Barbara: 45 year-old female

- 45 year-old administrative assistant; no routine exercise program outside of work.
- PMH
  - G2, P2, uncomplicated pregnancies
  - No known medical conditions
- PSH
  - Lumpectomy left breast – benign (2005)
  - T & A: childhood

Social history
- Nonsmoker; no second hand exposure
- 2 – 3 glasses white wine weekly
- FH
  - Father – alive and well; age 67
  - Mother – deceased; age 62 Alzheimer’s disease
  - Sister – alive and well; age 47
- Meds
  - MVI daily
  - Calcium 500 mg 1 tablet three times daily

Objective Data
- Height: 5’10”; Weight: 208 lbs
- BMI: 29.84
- Waist circumference: 38 inches
- Blood pressure: 139/88, 145/92
- Pulse: 86 beats per minutes
- Cardiac: RRR; PMI normal; no murmurs, no S3, no S4
- Pulses: DPPT – 2+ bilaterally; no edema
- EKG: RSR with 1st degree AV Block, LAD - 35 deg

CBC normal except RDW 15.7 (10.5-14%)
Glucose 113 (82-99 mg/dL)
BUN 23 (7-22 mg/dL)
Creatinine 0.98 (0.8-1.3 mg/dL)
Total Cholesterol 210 (<200 mg/dL)
HDL 37 (40-60 mg/dL)
LDL 145 (<130 mg/dL)
Triglycerides 169 (<150 mg/dL)
hs-CRP 2.9 (<2.0)
AST (SGOT) 67 (12-46 U/L)
ALT (SGPT) 87 (13-69 U/L)
Urine microalbumin 210 (<30)
AsC 6.4% (<6.0%)
GFR – MDRD 72 (>60 mL/min)

Barbara: Laboratory Data

- CBC WNL w RDW 15.7 (10.5-14%)
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- AsC 6.4% (<6.0%)
- GFR – MDRD 72 (>60 mL/min)
Barbara: Assessment...

<table>
<thead>
<tr>
<th>LABORATORY VALUE</th>
<th>RISK FOR CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social History</td>
<td>Risk for CAD</td>
</tr>
<tr>
<td>Waist Measurement</td>
<td>Risk for CAD</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Risk for CAD</td>
</tr>
<tr>
<td>EKG</td>
<td>Risk for CAD</td>
</tr>
<tr>
<td>Glucose</td>
<td>Risk for CAD</td>
</tr>
<tr>
<td>AsC</td>
<td>Risk for CAD</td>
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<td>HDL</td>
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</tr>
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<td>hsCRP</td>
<td>Risk for CAD</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Risk for CAD</td>
</tr>
<tr>
<td>Urine for Microalbumin</td>
<td>Marker of target organ damage</td>
</tr>
</tbody>
</table>

Risk evaluation...A Place to Begin!

- Metabolic Syndrome
  - Waist measurement
  - Insulin resistance
  - Impaired glucose tolerance/Impaired fasting glucose
  - Hypertension
  - Dyslipidemia (mixed)
  - Inflammation
  - Target organ damage

http://americanheart.org/presenter.jhtml?identifier=4756 Accessed 5-10-09

Goals for treatment

- Reduction of waist circumference: < 35 inches/40 inches
- Blood pressure: < 130/80 (JNCVII, NKF)
- HDL: > 50 mg/dL, > 60 mg/dL
- LDL: < 70 mg/dL vs. < 100 mg/dL
- Triglycerides: < 150 mg/dL
- Urine for microalbuminuria: (< 30 microU/ml)
- Improved MET level on treadmill
- Fasting glucose: < 100 mg/dL
- OGTT: < 140 mg/dL
- AsC: < 6.5% (AACE) < 7.0% (ADA)

http://www.americanheart.org/presenter.jhtml?identifier=536 Accessed 5-11-09

** Female/male references

Atherosclerotic plaque development

http://americanheart.org/presenter.jhtml?identifier=536 Accessed 5-11-09

** Female/male references
Endothelium

The endothelium is the largest organ in the body!

- Total Surface Area: About 6 tennis courts
- Total Mass: About 5 normal hearts
- Total Weight: Approx. 1800 grams (> liver)
- Total # Cells: About 1 trillion cells

Endothelium: The root cause?

- Injury to the endothelium appears to be the key event in:
  - The origin
  - The progression
  - The clinical manifestation of atherosclerotic plaques
- Endothelial dysfunction increases the likelihood for the presence of other risk factors

Risk factors for endothelial dysfunction

- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Diet
- Sedentary Lifestyle
- Oxidative Stress
- Heart Failure

Adapted from Vascular Biology Working Group, University of Florida College of Medicine, Carl Pepine, MD, Director
**Endothelium: Early diagnosis**

- Early diagnosis of endothelial issues is very similar to Class I classification of heart failure. "Patients at risk for development"
- Patients at risk for developing endothelial dysfunction
  - Insulin resistance
  - Dyslipidemia
  - Hypertension
  - Tobacco use


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**Insulin resistance**

- Defined clinically as a state in which a given increase in plasma insulin in an individual causes less of an effect in lowering the plasma glucose than it does in a normal population.


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**Prevalence of insulin resistance**

- Present in:
  - 25% of individuals with normal glucose levels
  - 59% of subjects with impaired fasting glucose
  - 88% of subjects with Type 2 diabetes

Metabolic syndrome consensus definition

- Three of the following:
  - Waist circumference: > 40 in. male / >35 in. female
  - Elevated triglycerides:
    - > 150 mg/dL (or treatment of triglycerides)
  - Reduced HDL-C:
    - <40 mg/dL (men) or < 50 mg/dL (women) or on treatment
  - Elevated blood pressure:
    - > 130 mm Hg systolic or > 85 mm Hg diastolic or on treatment
  - Raised FBS: >99 mg/dL or on treatment


Metabolic syndrome

- 47 million people in the USA have the metabolic syndrome.
  - Age 20 - 74 years old
    - Prevalence in men 24%; women 23.8%
  - Age 60 - 69 years old
    - Prevalence in men 43.5%; women 42%


Insulin resistance

- Adiposity and Physical Conditioning
  - 25% each...............50% of IR patients
  - BMI >25 = 66% are Insulin Resistant

- Genetic Factors............50% of IR Patients

First World Congress on Insulin Resistant Syndrome; 2003, Nov20-23, Los Angeles, California, USA

Factors which increase suspicion for presence of insulin resistance

- Cerebrovascular disease
- Hypertension
- PCOS
- NAFLD (NASH)
- Acanthosis nigricans
- Numerous skin tags
- Central adiposity
- Sedentary lifestyle
- Age > 40 years
- History of gestational diabetes
- Family history of diabetes

Insulin resistance: Why does it matter?

- A 30 year-old patient:
  - With insulin resistance:
    - 15% / 5-year risk of CAD
  - Without insulin resistance:
    - 5% / 10-year risk of CAD

Earliest hints of insulin resistance

Earliest Hint of Insulin Resistance

- Peripheral Insulin Resistance
- Fasting Glucose
- Plasma Insulin
- Glucose

Macrovascular Disease

Microvascular

Type II DM

Adapted from Robert Superko, MD, Berkeley Heart Lab, Inc.
Dyslipidemia
- Increase in VLDL, Small LDL
- Decrease in HDL (number and size)
NASH (hepatic manifestation of IR)
- ALT/AST > 1
- Increased Insulin levels
- > 30 microU/ml
Hypertension
- Systolic > 130 mmHg; Diastolic > 80 mmHg

Central Obesity
- Waist circumference
  - > 35 inches in women
  - > 40 inches in men
Glucose
- Normal glucose yet with multiple risk factors
  - ≥ 100 mg/dL
  - A1C ≥ 6.5%**

NASH (hepatic manifestation of IR)
- AL T/AST > 1
  - Ultrasound to verify absence of lesions
  - Hepatitis ABC screen
Proteinuria
- Spot urine for microalbuminuria > 30

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- ALT/AST > 1
  - Ultrasound to verify absence of lesions
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Proteinuria
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Barbara: Treatment Options
Barbara: Laboratory Data

- CBC normal except RDW: 15.7 (10.5-14%)
- Glucose: 113 (65-99 mg/dL)
- BUN: 23 (7-22 mg/dL)
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- ALT (SGPT): 87 (13-69 U/L)
- Urine microalbumin: 210 (<30)
- AsC: 6.2% (<6.0%)
- GFR – MDRD: 72 (>60 ml/min)

Suggested therapies for insulin resistance

- Diet
- Exercise
  - Stress test to stratify risk before starting exercise program?
- Weight loss
- Medications
  - Which one should we start first??

Definition: Hypertension

- A complex disease with a core defect of vascular dysfunction which may lead to target organ damage (TOD)
- Diagnosis:
  - 2 readings on 2 occasions in the absence of TOD
  - 1 reading in the presence of TOD

JNC VII. Hypertension. 2003;41:1178.
CV disease risk doubles with each 20/10 mm Hg BP increment*

CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure

*Individuals aged 40-70 years, starting at BP 115/75 mm Hg.


Framingham Data

``High-Normal'' BP in men and women is not benign

CV death, MI, stroke, heart failure. †Adjusted for concomitant CV risk factors.


Prehypertension (SBP 120-139 mm Hg or DBP 80-89 mm Hg)

Not at Goal BP (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease)

Stage 1 Hypertension (SBP 140-159 or DBP 90-99 mm Hg)
Thiazide-type diuretics for most; may consider ACEI, ARB, BB, CCB, or combination.

Stage 2 Hypertension (SBP ≥160 or DBP ≥100 mm Hg)
2-drug combinations for most (usually thiazide-type diuretics and ACEI, or ARB, or BB, or CCB).

Drug(s) for compelling indications
Other antihypertensive drugs (diuretic, ACEI, ARB, BB, CCB) as needed.

If not at goal BP, optimize dosage of all additional drugs until goal BP is achieved. Consider consultation with hypertension specialist.

Prevention of target organ damage

- Proteinuria
- Left ventricular hypertrophy
- Abnormal endothelial vascular responsiveness to stimuli
- May be more than just lowering the systolic and diastolic numbers

Evidence of target organ damage...

- Ventricular Hypertrophy
- Proteinuria
- CVA
- Vascular dementia
- CAD

Therapy for hypertension

- Initial Choices –
  - ACE
  - ARB
  - Direct renin inhibitor
  - Calcium channel blocker (non. vs. dihydopyridine)
  - Beta blocker
  - Thiazide diuretic
  - Aldosterone antagonist

JNC VII. Hypertension. 2003;41:1178.

Case Study

Hypertension Treatment

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Audience response

- What class of medication would you initiate first?

Dyslipidemia – Early diagnosis

- Screening guidelines:
  - Adults ≥ age 20 (ATP)
  - Children at risk – begin at age 2 (AAP)
  - Include:
    - family history
    - cardiovascular risk factors
    - assess for 'secondary risk' factors

Secondary causes of dyslipidemia

- Critical to clinical evaluation of a patient at risk for CVD
- Enhances our understanding of the patient's underlying disorders or risk to energy metabolism
- "4 D" - diet, drugs, disorders, diseases
- "Red Flags"
  - Progressive elevations in lipids in the absence of family history
  - Worsening lipids in spite of lifestyle or drug adherence
  - Unresponsive to medications to treat dyslipidemia
  - Life-threatening hyperlipidemia in a patient with previously mild or normal lipid values

Target organ damage...

- Proteinuria
- Retinopathy
  - AV nicking, plaques, hemorrhages
  - Retinal arteriolar sclerosis
- Coronary artery disease
- Cerebrovascular disease
- Chronic kidney disease
- Peripheral vascular disease

Statins: LDL lowering effects

<table>
<thead>
<tr>
<th>Statin</th>
<th>3A4</th>
<th>3A4</th>
<th>3A4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10 mg</td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>22%</td>
<td>31%</td>
<td>38%</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>22%</td>
<td>25%</td>
<td>31%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>34%</td>
<td>41%</td>
<td>46%</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20%</td>
<td>27%</td>
<td>32%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20%</td>
<td>25%</td>
<td>52%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20%</td>
<td>25%</td>
<td>51%</td>
</tr>
</tbody>
</table>

LDL
- Average individual < 100 mg/dL
- High risk individual < 70 mg/dL

HDL
- ATP III: >40 mg/dL – men; >50 mg/dL – women
- ADA: >45 mg/dL – men; >55 mg/dL – women
- Non-HDL-C (total cholesterol – HDL)
  - 30 mg/dL < LDL goal
- Triglycerides
  - Goal: <150 mg/dL

Therapy for dyslipidemia

<table>
<thead>
<tr>
<th>Class</th>
<th>Target of Impact</th>
<th>Mechanism/Effect of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>Liver</td>
<td>Decreases manufacturing LDL – lower LDL</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Gut</td>
<td>Binds bile acids in intestine impeding their reabsorption</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td>Brush border small intestine</td>
<td>Inhibit absorption of dietary cholesterol – Lower LDL</td>
</tr>
<tr>
<td>Nicotinic acid derivative</td>
<td>Liver</td>
<td>Prevents breakdown of HDL - increases HDL and decreases triglycerides</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Liver</td>
<td>Decreases triglycerides and increase HDL</td>
</tr>
<tr>
<td>Omega-3 acid ethyl esters</td>
<td>Liver</td>
<td>Decreases triglycerides</td>
</tr>
</tbody>
</table>

Secondary Causes of Dyslipidemia

- Drugs:
- Disorders/Diseases:
  - Obesity
  - Insulin resistance
  - PCOS
  - Male hypogonadism
  - Diabetes
  - Hypothyroidism
  - Nephrotic syndrome
  - Chronic liver disease
Reducing inflammation matters

Combination therapy

- Augmenting statin with....
  - Bile acid sequestrant
  - Cholesterol absorption inhibitor
  - Nicotinic acid
  - Omega-3
  - Fibrates

Lipid treatment matrix

<table>
<thead>
<tr>
<th>Issue</th>
<th>Statin</th>
<th>BAS</th>
<th>CAI</th>
<th>Niacin</th>
<th>Fibrate</th>
<th>Omega 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
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<tr>
<td># LDL</td>
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<tr>
<td>LDL Size</td>
<td>++++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>VLDL</td>
<td>+++</td>
<td>-/+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>++++</td>
<td>++</td>
<td></td>
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</tr>
</tbody>
</table>

Case Study

Dyslipidemia Treatment

Audience response

- Which therapy would you add on next?
  - A. Statin
  - B. Bile acid sequestrant
  - C. Fibrate
  - D. Niacin
  - E. Omega 3
  - F. Cholesterol absorption inhibitor

Diabetes
Target Organ damage
“Patient’s Perspective”

TARGET ORGAN DAMAGE
OUR PERSPECTIVE
Vascular Disease and Retinopathy

TARGET ORGAN DAMAGE
OUR PERSPECTIVE
Neuropathy Microalbuminuria

Target organ damage...

- Nephropathy
- Retinopathy
- Neuropathy
- Cardiovascular
  - MI
  - PAD
  - Cerebrovascular disease

Metascreen Writing Committee. Diabetes Care 2006;29:2701-2707
www.vbwg.org/journal_article.cfm?Article_ID=2266&template=search
Accessed 5-24-09

Diabetes
- Group of metabolic diseases characterized by hyperglycemia
  - It results from:
    - Defects in insulin secretion
    - Hepatic gluconeogenesis
    - Impaired action of insulin
    - Combination of the above


Classifications of diabetes
- Type 1 Diabetes
  - Beta Cell Destruction
  - Immune Mediated or Idiopathic
  - Accounts for 5 – 10% of all individuals with diabetes
- Type 2 Diabetes
  - Insulin resistance with a relative insulin secretory defect to complete insulin deficiency
  - Formerly referred to as adult onset
  - Vast majority are obese

**Classifications of diabetes**

- Slowly progressing type 1 or latent autoimmune diabetes in adults (Type 1.5)
  - Up to 20% of individuals labeled as T2DM actually have Type 1.5
  - 50% need insulin within 4 years of being diagnosed
- Characterized by presence of antibodies (GAD65) which destroy the pancreas
- Clues: thin, relatively young
- Usually no elevated blood pressure, normal triglycerides, normal HDL


**Classification and Diagnosis of DM**

- A1C
  - Lab using a method that is NGSP certified and standardized to the DCCT assay
  - A1c greater than or equal to 6.5% = diabetes
  - A1c 5.7 or greater = IFG
  - A1c 5.7 to 6.4 = individuals with high risk for future diabetes and to whom the term "pre-diabetes" may be applied

**Correlation of A1C with Glucose**

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Mg/dl</th>
<th>Mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
<td>7.0</td>
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<tr>
<td>7</td>
<td>154</td>
<td>8.6</td>
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<tr>
<td>8</td>
<td>183</td>
<td>10.2</td>
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<tr>
<td>9</td>
<td>212</td>
<td>11.8</td>
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<tr>
<td>10</td>
<td>240</td>
<td>13.4</td>
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<tr>
<td>11</td>
<td>269</td>
<td>14.9</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
<td>16.5</td>
</tr>
</tbody>
</table>

For every additional 29 points add 1%

**Classification and Diagnosis of DM**

- A1C – Quantifiers for Accuracy
  - Must use glucose criteria exclusively
  - Recent transfusions
  - Abnormal red blood cell turnover
    - Pregnancy
    - Anemias from hemolysis
    - Blood loss anemias
    - Significant and frequent hypoglycemias
    - Iron deficiency anemias
    - Use of erythropoietic products

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Therapies for diabetes

- Pancreas
  - Sulfonylureas
  - Meglitinides
  - DPP-4 inhibitors
  - Incretin Mimetics
- Liver
  - Biguanides
  - TZDs
  - DPP-4 inhibitors
  - Incretin Mimetics
  - Bile acid sequestrants
- Muscle and fat
  - Glucose level
  - Alpha-glucosidase inhibitors
  - Bile acid sequestrants

Case Study

Treatment Options

- What medication class would you initiate?
  - A. Sulfonylurea
  - B. Biguanide
  - C. TZD
  - D. Bile acid sequestrant
  - E. Incretin mimic
  - F. DPP-4 inhibitor
  - G. Insulin
  - H. Combination therapy

Approaches to CVD prevention

- Lipid modification
- Insulin Resistance Reduction
- Glucose lowering
- BP lowering

Optimal CV risk reduction