Aggressive Cholesterol Management to Prevent CHD in Diabetes

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Washington, D.C.
May 11, 2005
Prevalence of Diabetes in the United States

Mortality in People With Diabetes: Causes of Death

Atherosclerosis in Diabetes

- About 80% of all diabetic mortality (75% from coronary atherosclerosis; 25% from cerebral or peripheral vascular disease)
- >75% of all hospitalizations for diabetic complications
- >50% of patients with newly diagnosed NIDDM have CHD
Evolution of the Treatment Approach

1970s
- Framingham
- MRFIT
- LFC-CPPT
- Coronary Drug Project
- Helsinki Heart CLAS (anglo)

1988
- NCEP ATP I Guidelines
- Angiographic Trials (FATS, POSCH, SCOR, STARS, Omish, MARS)
- Meta-Analyses (Holme, Rossouw)

1993
- NCEP ATP II Guidelines

2001
- NCEP ATP III Guidelines
- 4S, WOSCOPS
- CARE,
- LIPID,
- AFCAPS/TexCAPS,
- VAHIT, Others

Evolution of the Treatment Approach
New Features of ATP III

- **CHD Risk Equivalents:**
  - 1. Type 2 Diabetes Mellitus
  - 2. Non-Cardiac Forms of Athero.
  - 3. Framingham Projection of 10 yr. Risk >20% (identifies individuals with multiple risk factors in need of more aggressive lipid lowering)

- The Metabolic Syndrome
Diabetes Mellitus As CHD Risk Equivalent

- Increased CHD Risk: Women -- 4-6 fold, Men-- >2 fold
- Risk for a person with DM having 1st MI is equal to a non-DM having 2nd MI
- DM more likely to die before reaching hospital with 1st MI
- DM confers worse prognosis in hospital and during first year after discharge
- >50% of DM have CHD at diagnosis
The Metabolic Syndrome

AKA:

- Pleuri-Metabolic Syndrome
- Insulin Resistance Syndrome
- Syndrome X (Metabolic)
- Deadly Quartet
- Multiple Metabolic Syndrome
The Metabolic Syndrome

General Features of the Metabolic Syndrome:

- Abdominal obesity
- Atherogenic dyslipidemia
  - Elevated triglycerides
  - Small Dense LDL particles
  - Low HDL cholesterol
- Raised blood pressure
- Insulin resistance (± glucose intolerance)
- Proatherosclerotic state
- Prothrombotic State
- Proinflammatory State
HAFFNER’S TICKING CLOCK HYPOTHESIS:

- The “Atherosclerosis Clock” starts ticking when Insulin Resistance develops.
- The “Clock” advances faster when hyperglycemia develops.
- The “Clock” begins to run-away when overt diabetes develops.
- Hence, by time of diagnosis, > 50% of DM have clinical CHD.
NHANES III Conclusions
The Metabolic Syndrome:

- Prevalence per ATP III definition
  - Overall: 23.7%
  - Mexican-Americans: highest age-adjusted
    - Prevalence: 31.9%

- 2000 census data
  - Approximately 47 million Americans

The Strong Heart Study

A study of cardiovascular disease in American Indians
supported by the National Heart, Lung, and Blood Institute
and the Indian Health Service
Prevalence of MS among non-diabetic American Indians, by age and gender, the Strong Heart Study, N=2,407

Prevalence (%)

- 45-54 (n=1277)
  - Men: 28.0
  - Women: 37.6
- 55-64 (n=731)
  - Men: 26.5
  - Women: 39.4
- 65-74 (n=399)
  - Men: 26.0
  - Women: 53.2
Prevalence of Diabetes
Strong Heart Study, by Gender and Center

%  

Women | Men

AZ | OK | ND/SD

Diabetes | IGT

0 | 20 | 40 | 60 | 80 | 100
Non-HDL Cholesterol
(Non-HDL Chol. = TC - HDL)

- Known predictor of CHD in epidemiology
- Equivalent to total apo B-100, and TC/HDL
- Represents the sum of LDL, Lp(a), IDL, and VLDL: All atherogenic apo B containing lipoproteins
- Lipid Equivalent of “HbA1C”
Guidelines for Treatment of Atherosclerosis in Patients with Diabetes

- Glycemic control
- Smoking cessation
- Lowering blood pressure
- Treatment of lipid abnormalities
- Weight reduction/Increase exercise

INSULIN RESISTANCE
HYPERINSULINISM

- Diabetes
- Hypertension
- Hyperlipidemia
- Atherosclerosis
Diabetes Prevention Program (DPP 2)

- Lifestyle changes consisting of diet and exercise reduced the conversion of IGT to Type 2 Diabetes by 58%

NEJM, 346; 393 2002
Effect of Pioglitazone on Lipid Levels

Mean change from baseline (%)

TG
Placebo
-9.0

HDL-C
15 mg
8.1

30 mg
14.1

Pioglitazone
45 mg
12.2

LDL-C
4.8

7.2

5.2

6.0

Treatment Modalities

INSULIN RESISTANCE-HYPERINSULINISM

Diabetes
- Diet
- ACE inhibitors
- Calcium channel blockers

Hypertension
- Alpha blockers
- Beta blockers
- Vasodilators

Hyperlipidemia

Atherosclerosis
HOT Trial
Effect of Diastolic Target on Cardiovascular Events - 4 Years

48% Risk Reduction

Events /1000 Pt-Yrs

Diabetic Patients
n=1, 501, P=0.016

Non-Diabetic Patients
n=18, 790, P=NS
Common Lipoprotein Abnormalities

Diabetic Dyslipidemia
CVD Hazard Ratios by Quartile of LDL Cholesterol in Diabetes
The Strong Heart Study

Howard et al. ATVB 2000;20(3):830
Cholesterol
— And Beyond

Statin Drugs Have Cut Heart Disease. Now They Show Promise Against Alzheimer’s, Multiple Sclerosis & Osteoporosis
The Pyramid of Recent Trials
Relative Size of the Various Segments of the Population

- Very high cholesterol with CHD or MI
- Moderately high cholesterol in high risk CHD or MI
- Normal cholesterol with CHD or MI
- High cholesterol without CHD or MI
- No history of CHD or MI

4S
LIPID
CARE
WOSCOP
AFCAPS/TexCAPS
## HMG CoA Reductase Inhibitors (Statins)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10–80 mg</td>
</tr>
<tr>
<td>Rosavustatin</td>
<td>5–40 mg</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>0.4–0.8 mg</td>
</tr>
</tbody>
</table>
Relation Between CHD Events and LDL-C in Recent Statin Trials

**Graph Description:**
- **X-axis:** Mean LDL-C level at follow-up (mg/dL)
- **Y-axis:** % with CHD event
- **Legend:**
  - CARE-Rx
  - LIPID-Rx
  - 4S-Rx
  - CARE-PI
  - LIPID-PI
  - AFCAPS/TexCAPS-PI
  - AFCAPS/TexCAPS-Rx
  - WOSCOPS-Rx
  - WOSCOPS-PI
  - 4S-PI

**Notes:**
- **1° Prevention**
- **2° Prevention**

**References:**

**Abbreviations:**
- PI = placebo
- Rx = treatment
Non-Statin Lipid Lowering Drugs

- Niacin—extended release, OTC immediate
- Bile Acid Sequestrants—colesevelam
- Fibric Acids—gemfibrozil, fenofibrate
- Intestinal acting—ezetimibe
- Omega 3 fatty acids—fish oil (EPA, DHA)
- Dietary adjuncts—plant sterol/stanol ester margerines, viscous fiber supplements
Rationale for Dual Inhibition Approach to Lipid Lowering

- Cholesterol metabolism is a complex process involving multiple pathways
- Two main sources of cholesterol: ingested and produced endogenously
- Body processes cholesterol via 2 main pathways: production and absorption
- Modulate cholesterol metabolism on 2 fronts:
  - Cholesterol production
  - Cholesterol absorption
- Achieve significant LDL-C reductions through dual inhibition
Fig. 14. Rationale for the use of a bile acid–binding resin and an inhibitor of HMG CoA reductase in the treatment of FH heterozygotes.
Mechanism of Intestinal-Acting Agents
Ezetimibe: Inhibition of Cholesterol Absorption

Liver

Duodenum
Jejunum
Ileum
Colon

VLDL Apo B100

CM Remnant Apo B48

CM Apo B48

LDL Apo B100

Ezetimibe Inhibits Absorption

Adapted with permission from Carey MC, Duane WC. In: Arias IM et al, eds. The Liver: Biology and Pathobiology. Raven Press; 1994.
Dosage and Administration

- Patients should be on a standard cholesterol-lowering diet*
- Dosage should be individualized according to baseline LDL-C, recommended goal of therapy, and patient response*
- Dosage range: 10/10 mg/day–10/80 mg/day
- Usual recommended starting dose: 10/20 mg/day
- Patients requiring a larger reduction in LDL-C (>55%) may be started at a dose of 10/40 mg/day; 10/10 mg/day can be increased in 4-week intervals until the desired LDL-C level is achieved.*
VYTORIN Lowered LDL-C by 52% at the Starting Dose

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>10/20 mg (n = 156)</th>
<th>10/40 mg (n = 147)</th>
<th>10/80 mg (n = 154)</th>
</tr>
</thead>
</table>

- VYTORIN lowered LDL-C more than simvastatin across the dosage range
- Simvastatin lowered LDL-C by 34% at the 20-mg dose, 41% at the 40-mg dose, and 49% at the 80-mg dose

<table>
<thead>
<tr>
<th>VYTORIN 10/20 mg mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C 176 mg/dL</td>
</tr>
<tr>
<td>Mean End Point LDL-C  84 mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VYTORIN 10/80 mg mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C 178 mg/dL</td>
</tr>
<tr>
<td>Mean End Point LDL-C  70 mg/dL</td>
</tr>
</tbody>
</table>
VYTORIN Provided Significantly Greater LDL-C Reductions vs Atorvastatin

Starting Doses (mg)

<table>
<thead>
<tr>
<th></th>
<th>10/20</th>
<th>10/40</th>
<th>10/80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10 mg</td>
<td>10 (n = 262)</td>
<td>10/40 mg (n = 482)</td>
<td>10/80 mg (n = 459)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VYTORIN 10/20 mg</td>
<td>20 (n = 246)</td>
<td>40 mg (n = 237)</td>
<td>80 mg (n = 228)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-50%*</td>
<td>-56%†</td>
<td>-59%‡</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 for VYTORIN 10/20 vs atorvastatin 10 mg; P≤0.05 for VYTORIN 10/20 vs atorvastatin 20 mg.
†P≤0.05 for VYTORIN 10/40 vs atorvastatin 40 mg.
‡P<0.001 for VYTORIN 10/80 vs atorvastatin 80 mg.

The clinical significance of comparative lipid effects has not been established.
VYTORIN Provided Excellent HDL-C Efficacy

**Starting Doses (mg)**

<table>
<thead>
<tr>
<th></th>
<th>10/20 (n = 250)</th>
<th>10 (n = 262)</th>
<th>20 (n = 246)</th>
<th>10/40 mg (n = 482)</th>
<th>40 mg (n = 237)</th>
<th>10/80 mg (n = 459)</th>
<th>80 mg (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Increase in HDL-C From Untreated Baseline, %</td>
<td>9%*, †</td>
<td>7%</td>
<td>5%</td>
<td>11%*</td>
<td></td>
<td>12%‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>8%</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P ≤ 0.05 for VYTORIN 10/20 mg vs atorvastatin 10 mg and for VYTORIN 10/40 mg vs atorvastatin 40 mg.
†P = NS for VYTORIN 10/20 vs atorvastatin 20 mg.
‡P < 0.001 for VYTORIN 10/80 vs atorvastatin 80 mg.

The clinical significance of raising HDL-C has not been established.
COMPARATIVE COST per Month

- Vytorin 10/10,20,40,80 $84.24
- Zetia 77.77
- Zocor 10 mg. 79.02
- 20 mg. 137.87
- 40 mg. 137.87
- 80 mg. $ 137.87

Medical Letter (9/13/04); 46,73,2004
GREek Atorvastatin and Coronary Heart Disease Evaluation Study

GREACE TRIAL

Current Medical Research and Opinions, 2002; 18: 220-227
GREACE TRIAL

RESULTS:

- Total Mortality: -43%
  - CHD Mortality: -47%
  - non fatal MI: -59%
  - Revascularization: -51%
  - CHF: -50%
  - Stroke: -47%
  - Women: -54%
  - Diabetics: -58%
  - 60-75 yoa: -49%
Heart Protection Study (HPS) Design

- Large, multicenter, placebo-controlled, double-blind study
- Mean duration: 5 years
- Patients (N=20,536, 97% Caucasian) allocated* to
  - Simvastatin 40mg/day (n=10,269)
  - Placebo (n=10,267)
- Mean age 64 years (range 40 to 80 years)
- Patients were at high risk of a major coronary event because of
  - Existing coronary heart disease (CHD) (65%)
  - Diabetes (type 2, 26%; type 1, 3%)
  - History of stroke or other cerebrovascular disease (16%)
  - Peripheral vessel disease (33%)
  - Hypertension in males aged 65 years and older (6%)

* Patients were allocated to treatment using a covariate adaptive method, which took into account the distribution of 10 important baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups.
## HPS: MCE by Metabolic History

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>n</th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>MCE Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>5,963</td>
<td>9.4</td>
<td>12.6</td>
<td>Favors placebo</td>
</tr>
<tr>
<td>Without CHD</td>
<td>3,982</td>
<td>5.5</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>With CHD</td>
<td>1,981</td>
<td>17.4</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>Without diabetes mellitus</td>
<td>14,573</td>
<td>8.5</td>
<td>11.5</td>
<td></td>
</tr>
</tbody>
</table>
HPS: Primary and Secondary Prevention Implications

LDL-C is Closely Related to CHD Events

CHD + Revasc + Stroke (HPS = CHD Only)
Solid Shapes = Drug Rx
Outline Shapes = Placebo

CHD Events, %
30%
25%
20%
15%
10%
5%
0%

Mean On-Treatment LDL-C Level at Follow-Up (mg/dL)
40
60
80
100
120
140
160
180
200

1° Prevention
2° Prevention

1. Adapted from Ballantyne CM. Low-density lipoproteins and risk for coronary artery disease. Am J Cardiol. 1996;82:3Q–12Q, with permission from Excerpta Medica.
New Category: Very High Risk Patients

- Definite CHD plus additional risk factors, such as diabetes, significant hypertension etc.
- LDL goal < 100 mg/dl with optional goal of <70 mg/dl.
- Initiate drug therapy if LDL > 100 mg/dl with consideration for drug therapy to reach optional goal of < 70 mg/dl when baseline LDL < 100mg/dl
- Lower LDL by at least 30%.

Circulation 2004;110:227-239
Primary Prevention Study: 2838 T2DM randomized atorva. 10 mg. or placebo. (+ Additional risk factor)
Terminated at 3.9 years—2 years early.
End of study LDL: atorva = 78 mg/dl and placebo = 120 mg/dl.
End of Study non-HDL: atorva = 100 mg/dl and placebo = 155 mg/dl.
No excess of adverse events in atorvastatin group
CARDS RESULTS

- All Cause Mortality: - 27 %
- CHD Events: - 36 %
- Revascularizations: - 31 %
- Stroke: - 48 %

Lancet 2004: 364; 685-696
Clinical Trials of Lipid Lowering to Prevent CHD in Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS</td>
<td>Prevention</td>
</tr>
<tr>
<td>ALL HAT</td>
<td>No Prevention</td>
</tr>
<tr>
<td>ASCOT</td>
<td>No Prevention</td>
</tr>
<tr>
<td>CARDS</td>
<td>Prevention</td>
</tr>
</tbody>
</table>
SANDS

- Stop
- Atherosclerosis in Native Diabetics Study
What we learned from SHS

- Most CVD in SHS communities occurs in those with diabetes
- LDL cholesterol is a strong predictor even though levels are generally low in Indians
- Blood pressure is a strong predictor, and it leads to nephropathy which also causes CVD
Inclusion Criteria

- Diabetic Men and Women >40 yrs
- LDL>100 mg/dl
- SBP>130 mm
- Able to measure carotid IMT
Four Clinical Centers

- Phoenix area (Charlton Wilson, MD, Marie Russell, MD, Damon Davis, RN)
- Oklahoma (Brice Poolaw, MD)
- South Dakota (Jeffrey Henderson, MD)
- Chinle (Jim Galloway, MD)

- 496 Men and Women (124/center)
HYPOTHESIS

Lowering LDL cholesterol and Blood Pressure to lower targets than are currently recommended will retard CVD

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL chol (mg/dl)</td>
<td>&lt;100</td>
<td>&lt;70</td>
</tr>
<tr>
<td>SBP (mm)</td>
<td>130/80</td>
<td>115/75</td>
</tr>
</tbody>
</table>
Men and women with diabetes over 40 yrs old

Usual targets

Measure CVD using carotid and cardiac ECHO at baseline and after 3 yrs FU

Lower targets
Algorithm for LDL Therapy

A

1. LDL > target

   Statin (Dose per LDL level)

   LDL < target
   Non HDL < target

   Monitor

   LDL < target
   Non HDL > target

   Fish Oil

   Follow Protocol B

   LDL < target
   Non HDL < target

   Monitor

   LDL < target
   Non HDL > target

   Increase Statin

   Follow Protocol B

   LDL < target

B

1. LDL < target
   Non HDL > target

   Fish Oil

   Add Fenofibrate or Niacin

   Monitor

   LDL < target
   Non HDL > target

   Follow Protocol B

   LDL < target
   Non HDL < target

   Monitor
SUMMARY

- There is a rising tide of CVD in diabetes
- LDL and blood pressure are strong risk factors
- We believe SANDS will validate a strategy to prevent/retard CVD in diabetes
- SHS will continue to work to identify future strategies for therapy or prevention of CVD in diabetes
Diabetes and an Excess of Fat

“With an excess of fat diabetes begins and from an excess of fat diabetics die…”

- EP Joselin, 1927
Insulin Resistance: Inherited and Acquired Influences

Inherited
- Rare mutations
  - Insulin receptor
  - Glucose transporter
  - Signaling proteins
- Common forms
  - Largely unidentified

Acquired
- Inactivity
- Overeating
- Aging
- Medications
- Hyperglycemia
- Fatty acids

Insulin Resistance
Comprehensive Medical Therapy For Patients with CHD or Other Vascular Disease

- ASA 20-30%
- Beta Blockers 20-35%
- ACE inhibitors 22-25%
- Statins 25-50%

The four medications every atherosclerosis patient should be treated with, unless contraindications exist and are documented.

Adapted from the UCLA CHAMP Guidelines 1994
CHAMP ~ Impact on Clinical Outcomes in the First Year Post Hospital Discharge

256 AMI pts discharged in 92/93 pre-CHAMP compared to 302 pts in 94/95 post-CHAMP
ASA 78% vs 92%; Beta Blocker 12% vs 61%; ACEI 4% vs 56%; Statin 6% vs 86%
Fonarow Am J Cardiol 2001;87;819-822

Death or Recurrent MI %

RR 0.43
p<0.01