Aggressive Lipid Management to Prevent CHD in Diabetes

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Prevalence of Obesity in the United States

1991

2000

Legend:
- No Data
- <10%
- 10%-14%
- 15%-19%
- ≥20%

Prevalence of Diabetes in the United States

1990

2000

No Data
<4%
4%–6%
>6%

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)

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

NCEP ATP II Guidelines 1993

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

**LDL Cholesterol (mg/dL)**

- <100  Optimal
- 100–129  Near optimal/above optimal
- 130–159  Borderline high
- 160–189  High
- ≥190  Very high
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
The Metabolic Syndrome as a Secondary Target of Therapy

General Features of the Metabolic Syndrome

- Abdominal obesity
- Atherogenic dyslipidemia
  - Elevated triglycerides
  - Small LDL particles
  - Low HDL cholesterol
- Raised blood pressure
- Insulin resistance (± glucose intolerance)
- Proatherosclerotic state
- Prothrombotic state
- Proinflammatory state
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 of Diabetes
Strong Heart Study, by Gender and Center

% of Population

Women
Men

AZ
OK
ND/SD

Diabetes
IGT
Non-HDL Cholesterol (Non-HDL Chol. = TC - HDL)

- Known predictor of CHD in epidemiology
- Represents the sum of LDL, Lp(a), IDL, and VLDL: All atherogenic apo B containing lipoproteins
- Lipid Equivalent of “HbA1C”
Comparison of LDL-C and Non-HDL-C Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>Non-HDL-C Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD Risk Equivalent (10-year risk for CHD &gt;20%)</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Multiple (2+) Risk Factors and 10-year risk &lt;20%</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>
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
Relation Between CHD Events and LDL-C in Recent Statin Trials

Mean LDL-C level at follow-up (mg/dL) vs % with CHD event

1° Prevention

AFCAPS/TexCAPS-PI
WOSCOPS-Pi

2° Prevention

CARE-Rx
LIPID-Rx
4S-Rx
LIPID-PI
4S-PI

CARE-PI
AFCAPS/TexCAPS-Rx
WOSCOPS-Rx

PI=placebo; Rx=treatment

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>Incidence(%)</th>
<th>MCE Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Simvastatin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5,963</td>
<td>9.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Without CHD</td>
<td>3,982</td>
<td>5.5</td>
<td>8.4</td>
</tr>
<tr>
<td>With CHD</td>
<td>1,981</td>
<td>17.4</td>
<td>21.0</td>
</tr>
<tr>
<td>Without diabetes mellitus</td>
<td>14,573</td>
<td>8.5</td>
<td>11.5</td>
</tr>
</tbody>
</table>

The diagram illustrates the comparison of MCE risk ratios between Simvastatin and Placebo across different baseline characteristics. The risk ratios favor Simvastatin for Diabetes mellitus and Without CHD, and Placebo for With CHD and Without diabetes mellitus.
**SIMVASTATIN: VASCULAR EVENT by LDL**

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>STATIN (10269)</th>
<th>PLACEBO (10267)</th>
<th>Risk ratio and 95% CI</th>
<th>STATIN better</th>
<th>STATIN worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 (2.6 mmol/l)</td>
<td>285</td>
<td>360</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100 &lt; 130</td>
<td>670</td>
<td>881</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 130 (3.4 mmol/l)</td>
<td>1087</td>
<td>1365</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Het $\chi^2 = 0.8$

24%SE 2.6 reduction (2P<0.00001)
Implications of Recent Clinical Trials for ATP III Goals

- Recent trials provide greater rationale for lower target LDL-C levels and more intensive LDL-lowering therapy.
- Key modifications to ATP III treatment algorithm for LDL-C:
  - LDL-C goal <70 mg/dL is therapeutic option for patients at very high risk.
  - Addition of fibrate or nicotinic acid should be considered for high-risk patients with high TG or low HDL-C.
  - LDL-C goal <100 mg/dL is therapeutic option for moderately high-risk patients.
  - At least 30% to 40% reduction in LDL-C recommended for high-risk and moderately high-risk patients.

LDL-C Is Closely Related to CHD Events

# 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>
Percentage Change in LDL-C: Pairwise Comparisons

The STELLAR Trial

STELLAR = Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin.

*P<.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg.

**P<.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg.

†P<.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg.

Adapted from Jones et al. Am J Cardiol 2003;92:152-160.
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
REMAINING QUESTION:

What Should be the Goal for LDL-C and non-HDL-C for Primary CHD Prevention in Type 2 Diabetes Mellitus???
<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
Four Clinical Centers

- **Phoenix** (Charlton Wilson, MD; Marie Russell, MD)
- **Oklahoma** (Brice Poolaw, MD)
- **South Dakota** (Jeffrey Henderson, MD)
- **Chinle** (James Galloway, MD)

496 Men and Women (124/center)
HYPOTHESIS and DESIGN

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

Duration—3 years.

<table>
<thead>
<tr>
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<th>Control</th>
<th>Interv.</th>
</tr>
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<tbody>
<tr>
<td>LDL chol (mg/dl)</td>
<td>&lt;100</td>
<td>&lt;70</td>
</tr>
<tr>
<td>SBP (mm/Hg)</td>
<td>130/80</td>
<td>115/75</td>
</tr>
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</table>

- Primary End Points: Carotid IMT and Echo Cardiography.
- Secondary: Clinical Outcomes
Inclusion Criteria

- Diabetic Men and Women >40 yrs without CHD
- LDL > 100 mg/dl
- SBP > 130 mm
- Able to measure carotid IMT
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

STRONG HEART will continue to work to identify future strategies for therapy or prevention of CVD in diabetes
“Good” Cholesterol
Encouraging News for Your Heart
Anti-atherothrombotic Actions of HDL

- Enhanced Reverse Cholesterol Transport
- Anti-oxidant
- Anti-thrombotic:
  - antiplatelet
  - protein C activation
- Pro-fibrinolytic
- Anti-inflammatory

Anti-atherothrombotic effect
Diabetes and an Excess of Fat

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

- EP Joselin, 1927
PROVE IT

- 4162 CHD Patients Randomized to Pravastatin 40 vs. Atorvastatin 80 Followed for 2 1/2 Years
- Pravastatin---LDL decreased from 106 to 95 mg/dl
- Atorvastatin--LDL decreased from 106 to 62 mg/dl
- Atorvastatin showed added benefit vs. Pravastatin:
  - 16% decrease in Angina, Revasc., & MI
  - 30% decrease in CHD Death
  - 28% decrease in Total Mortality
  - *Benefit seen within 30 Days*
TNT: Design

Patient population
- 250 centers in 14 countries (N = 10,001)
- LDL 130–250 mg/dL
- TG <600 mg/dL

Atorvastatin 10 mg
8 weeks

Atorvastatin 10 mg

Atorvastatin 80 mg
4.9 years

TNT: Treatment effects on primary outcome

Major CV events (%)

0.00 0.05 0.10 0.15 0.20

0 1 2 3 4 5 6

Years

Atorvastatin 10 mg

22% risk reduction

Atorvastatin 80 mg

HR = 0.78 (0.69–0.89)
P < 0.001

CARDS

- 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
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

Death or Recurrent MI %

Pre-CHAMP vs Post-CHAMP

RR 0.43
p<0.01

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
### Algorithm for LDL Therapy

**A**

- **LDL > target**
  - **Statin** (Dose per LDL level)
    - **LDL < target**
      - **Non HDL < target**
        - **Monitor**
        - **Fish Oil**
        - Follow Protocol B
    - **LDL < target**
      - **Non HDL > target**
        - **Fish Oil**
        - **Increase Statin**
        - **Follow Protocol B**
    - **LDL > target**
      - **Monitor**

**B**

- **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**