Clinical Symposium

Hyperlipidemia

Chairman
Antonino Cartabellotta (Palermo, Italy)

Participants
Angela Rivellese (Naples, Italy)
Om Ganda (Boston, USA)
Clinical scenario (1)

- AP, housewife, age 58 yrs

- **Family history**
  - No hyperlipidemia, father, type 2 diabetes and fatal MI at age 70 yrs

- **Personal history**
  - Non smoker, no alcohol, menopause at age 54 yrs
  - Type 2 diabetes since 5 yrs, treated with low calorie diet (with satisfactory compliance) and metformin 1000 mg x 3
  - Hypertension diagnosed two years before and well controlled with ramipril 20 mg/die
Clinical scenario (2)

• Physical examination

- Weight 61 kg
- BMI 27
- Waist circumference cm 84
- BP 130/85 mmHg
- No clinical or instrumental evidence of cardiovascular diseases
Clinical scenario (3)

• Daily blood glucose profile
  - Fasting 200 mg/dl
  - Before lunch 180 mg/dl
  - 2 h after lunch 210 mg/dl
  - Before dinner 160 mg/dl
  - 2 h after dinner 180 mg/dl

• HbA1c 8.0 %
• Microalbuminuria 100 mg/day

• Lipid profile
  - Serum cholesterol 260 mg/dl
  - Serum triglycerides 320 mg/dl
  - HDL cholesterol 22 mg/dl
  - LDL cholesterol 186 mg/dl (Friedwald’s formula)

• Normal liver and renal functions
Mixed hyperlipidemia in overweight patient with poorly controlled type 2 diabetes and hypertension
Therapeutic decision

• To optimize the blood glucose control, the patient start bedtime intermediate insulin (14 UI s.c.)
Clinical scenario (4)

After six months
- Body weight: increased of 3 kg
- Blood pressure: 130/85 mmHg
- HbA1c: 7%
- Daily blood glucose profile: good
- Renal and liver function: normal
- Lipid profile

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol</td>
<td>260</td>
<td>240</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>320</td>
<td>260</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>186</td>
<td>163</td>
</tr>
</tbody>
</table>
CLINICAL QUESTIONS
1. What is your estimate about 5 years cardiovascular risk of the patient?

1. < 10%  (mild)
2. 10-15%  (moderate)
3. 15-20%  (high)
4. > 20%   (very high)
### DIABETES

#### Risk Level:

- **Five-year CVD risk (non-fatal and fatal)**
  - Very High: >30%
  - High: 25–30%
  - Moderate: 20–25%
  - Mild: 15–20%
  - <2.5%

#### Blood Pressure:

<table>
<thead>
<tr>
<th>Age</th>
<th>Nonsmoker</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio of Total Cholesterol:HDL</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td></td>
<td>4 5 6 7 8</td>
<td>4 5 6 7 8</td>
</tr>
<tr>
<td>70</td>
<td>[Grid]</td>
<td>[Grid]</td>
</tr>
<tr>
<td>60</td>
<td>[Grid]</td>
<td>[Grid]</td>
</tr>
</tbody>
</table>

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Adler AI, Stratten IM, Holman RR, et al.

The UKPDS Risk Engine
A model for the risk of coronary heart disease in type 2 diabetes

Clinical Science 2001;101:671-679
Age now: 58 years
Diabetes duration: 5 years
HbA1c: 8.0%
Systolic BP: 130 mm Hg
Sex: Female
Total cholesterol: 6.7 mmol/l
Atrial fibrillation: No
HDL cholesterol: 0.57 mmol/l
Ethnicity: White
Smoking: Non-smoker

5 year risk:
Coronary heart disease: 13.0%
Stroke: 2.8%
95% confidence interval:
Coronary heart disease: 9.7% - 16.3%
Stroke: 1.2% - 4.3%

Adjusted for regression dilution
UKPDS Risk Engine v1.0

Input
- Age now: 56 years
- HbA1c: 8.0%
- Diabetes duration: 5 years
- Systolic BP: 130 mm Hg
- Sex: Female
- Total cholesterol: 6.7 mmol/l
- Atrial fibrillation: No
- HDL cholesterol: 0.57 mmol/l
- Ethnicity: White
- Smoking: Non-smoker

Output
- 10 year risk
  - Coronary heart disease: 28.9%
  - Stroke: 8.0%
- 95% confidence interval
  - Coronary heart disease: 22.1% - 35.7%
  - Stroke: 3.6% - 12.3%

Adjusted for regression dilution

Calculate  Help  Exit
**Information about your risk score:**

<table>
<thead>
<tr>
<th>Age:</th>
<th>58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td>Female</td>
</tr>
<tr>
<td>Total Cholesterol:</td>
<td>260 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol:</td>
<td>22 mg/dL</td>
</tr>
<tr>
<td>Smoker:</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure:</td>
<td>130 mm/Hg</td>
</tr>
<tr>
<td>On medication for HBP:</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Risk Score</strong></td>
<td><strong>11%</strong></td>
</tr>
</tbody>
</table>

Means 11 of 100 people with this level of risk will have a heart attack in the next 10 years.

* Your risk score was calculated using an equation. Other NCEP products, such as printed ATP III materials, use a point system to determine a risk score that is close to the equation score.

To find out what your risk score means and how to lower your risk for a heart attack, go to "**High Blood Cholesterol—What You Need to Know**" and visit the "**Live Healthier, Live Longer**" Web site.
DONNE CON DIABETE

NON FUMATRICI

Colesterolemia

mg/dl

mmol/l

4 5 6 7 8

180 160 140 120

FUMATRICI

Colesterolemia

mg/dl

mmol/l

4 5 6 7 8

180 160 140 120

LIVELLO DI RISCHIO

basso <5%

moderato 10-20%

elevato 20-40%

molo alto >40%

Pressione arteriosa sistolica (mmHg)

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Dont’ forget!

Current assessment methods may underestimate risk in diabetics with microalbuminuria
Lowering cholesterol in diabetic patients

What say practice guidelines?

- American Diabetes Association, 2002
- ATPIII, 2001
- SIGN, 1999
<table>
<thead>
<tr>
<th></th>
<th>Medical nutrition therapy</th>
<th>Drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initiation level</td>
<td>LDL goal</td>
</tr>
<tr>
<td>With CHD, PVD, or CVD</td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Without CHD, PVD, and CVD</td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

Data are given in milligrams per deciliter. *For patients with LDL between 100 and 129 mg/dl, a variety of treatment strategies are available, including more aggressive MNT and pharmacological treatment with a statin; in addition, if the HDL is <40 mg/dl, a fibrin acid such as fenofibrate may be used in these patients. MNT should be attempted before starting pharmacological therapy. PVD, peripheral vascular disease.
Since diabetes is designated a CHD risk equivalent in ATP III, the LDL cholesterol goal of therapy for most persons with diabetes will be ≤100 mg/dL.


**Table 5. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)</th>
<th>LDL Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents (10-year risk ≥20%)</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥130 (100-129: drug optional)†</td>
</tr>
<tr>
<td>2+ Risk factors (10-year risk ≤20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10%-20%: ≥130</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-year risk &lt;10%: ≥160</td>
</tr>
<tr>
<td>0-1 Risk factor‡</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190 (160-189: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

*LDL indicates low-density lipoprotein; CHD, coronary heart disease.
†Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g. nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
‡Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.
• Lipid lowering drug therapy should be considered for primary prevention in Type 2 diabetics without evidence of nephropathy when the 10 year risk of a major coronary event is >=30% using the Joint British Coronary Coronary Chart.

• Lipid lowering drug therapy should be considered at a lower risk threshold in diabetics with nephropathy.
But…

what is the evidence base of practice guidelines?
The observational evidence as base for aggressive treatment of cardiovascular risk factors in diabetics

No diabetes and myocardial infarction

= 

Diabetes without myocardial infarction

↓

Secondary prevention in non diabetics

= 

Primary prevention in diabetics

Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction

Figure 1. Kaplan–Meier Estimates of the Probability of Death from Coronary Heart Disease in 1059 Subjects with Type 2 Diabetes and 1378 Nondiabetic Subjects with and without Prior Myocardial Infarction. MI denotes myocardial infarction. I bars indicate 95 percent confidence intervals.
Evans JMM, Wang J, Morris AD.

Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction. Cross sectional and cohort studies.

BMJ 2002;324:939-42
**Fig 2** Kaplan-Meier survival curve showing time to death from cardiovascular causes in patients with newly diagnosed type 2 diabetes and patients who had just had a myocardial infarction (MI).
Primary prevention of CAD in diabetic patients
Evidence from lipid lowering drug trials

1. Direct evidence
2. Subgroup analyses of RCTs
3. In progress studies
1. Direct evidence

<table>
<thead>
<tr>
<th>RCT</th>
<th>Drug</th>
<th>Outcome</th>
<th>Years</th>
<th>Event/pts</th>
<th>Event/pts</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENDCAP</td>
<td>Bezafibrate</td>
<td>MI or new ischaemic changes on ECG</td>
<td>3</td>
<td>5/64</td>
<td>16/64</td>
<td>6 (5 to 20)</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAIS</td>
<td>Micronized Fenofibrate</td>
<td>Death or MI</td>
<td>3.8</td>
<td>15/207</td>
<td>21/111</td>
<td>NS</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary prevention of CAD in diabetic patients
Evidence from lipid lowering drug trials

1. Direct evidence
2. Subgroup analyses of RCTs
3. In progress studies
2. Subgroup analyses of RCTs

Until 2002

• Most published clinical trials, with sufficient power to detect effects on cardiovascular events, have enrolled comparatively few people with diabetes, or have excluded them.

• Subgroup analyses of results for people with diabetes enrolled into large RCTs have found that statins or fibrates versus placebo reduce risk of acute myocardial infarction in people with diabetes and dyslipidaemia.
# 2. Subgroup analysis of RCTs

## Until 2002

<table>
<thead>
<tr>
<th>RCT</th>
<th>Drug</th>
<th>Outcome</th>
<th>Years</th>
<th>Treated Events/pts</th>
<th>Controls Events/pts</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Lovastatin</td>
<td>MI, unstable angina, or sudden cardiac death</td>
<td>5</td>
<td>4/84</td>
<td>6/71</td>
<td>NS</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin</td>
<td>Non-fatal myocardial infarction and death from coronary heart disease</td>
<td>4.9</td>
<td>60/598*</td>
<td>70/596*</td>
<td>NS</td>
</tr>
<tr>
<td>Helsinki</td>
<td>Gemfibrozil</td>
<td>MI or cardiac death</td>
<td>5</td>
<td>2/59</td>
<td>8/76</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Patients with two or more risk factors (smoking, hypertension, a history of chest pain or intermittent claudication, diabetes, and a minor ECG abnormality). The diabetic men were only 76.
Horton R

From star signs to trial guidelines

Lancet 2000;355:1033-4
<table>
<thead>
<tr>
<th>Astrological birth sign</th>
<th>Vascular death by 1 month</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Libra or Gemini</td>
<td>150 (11·1%)</td>
<td>147 (10·2%)</td>
<td>0.5</td>
</tr>
<tr>
<td>All other signs</td>
<td>654 (9·0%)</td>
<td>869 (12·1%)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Any birth sign</td>
<td>804 (9·4%)</td>
<td>1016 (11·8%)</td>
<td>&lt;0·0001</td>
</tr>
</tbody>
</table>

Table 3: Unreliability of “data-dependent” subgroup analyses: ISIS-2 trial of aspirin among over 17 000 patients with suspected acute myocardial infarction²³
The credibility of subgroup analyses is improved if:

- It is pre-planned
- It is confined to the primary outcome
- There are few predefined subgroups, on the basis of biologically plausible hypotheses.
- It is numerically consistent
1. Subgroup analyses of RCTs

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial

Heart Protection Study Collaborative Group*
### Simvastatin-allocated vs Placebo-allocated

<table>
<thead>
<tr>
<th>Condition</th>
<th>Simvastatin-allocated</th>
<th>Placebo-allocated</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Cerebrovascular</td>
<td>172/922 (18.7%)</td>
<td>212/898 (23.6%)</td>
</tr>
<tr>
<td>+ Peripheral vascular</td>
<td>327/1325 (24.7%)</td>
<td>420/1376 (30.5%)</td>
</tr>
<tr>
<td>+ Diabetes mellitus</td>
<td>276/2006 (13.8%)</td>
<td>367/1976 (18.6%)</td>
</tr>
<tr>
<td><strong>Subtotal: no CHD</strong></td>
<td><strong>574/3575 (16.1%)</strong></td>
<td><strong>744/3575 (20.8%)</strong></td>
</tr>
</tbody>
</table>

- Relative risk reduction: 26% (14-38)
- Number needed to treat: 21 (14-40)

but....
<table>
<thead>
<tr>
<th>Characteristic at entry</th>
<th>Type 1 (n=615)</th>
<th>Type 2 (n=5348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>30 (5%)</td>
<td>1095 (20%)</td>
</tr>
<tr>
<td>Other CHD</td>
<td>31 (5%)</td>
<td>822 (15%)</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>124 (20%)</td>
<td>948 (18%)</td>
</tr>
<tr>
<td>No cardiovascular</td>
<td>430 (70%)</td>
<td>2483 (46%)</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>118 (19%)</td>
<td>2279 (43%)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>28.6 (0.5)</td>
<td>9.3 (0.1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65</td>
<td>564 (92%)</td>
<td>3082 (58%)</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>51 (8%)</td>
<td>2266 (42%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5.5</td>
<td>315 (51%)</td>
<td>2464 (46%)</td>
</tr>
<tr>
<td>&gt; 5.5 ≤ 7.0</td>
<td>257 (42%)</td>
<td>2349 (44%)</td>
</tr>
<tr>
<td>&gt; 7.0</td>
<td>43 (7%)</td>
<td>535 (10%)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3.0</td>
<td>330 (54%)</td>
<td>2131 (40%)</td>
</tr>
<tr>
<td>&gt; 3.0 ≤ 3.5</td>
<td>113 (18%)</td>
<td>1306 (24%)</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>172 (28%)</td>
<td>1911 (36%)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1.0</td>
<td>96 (16%)</td>
<td>3023 (57%)</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>519 (84%)</td>
<td>2325 (43%)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2.0</td>
<td>526 (86%)</td>
<td>2690 (50%)</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>89 (14%)</td>
<td>2658 (50%)</td>
</tr>
<tr>
<td>HbA1c (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 7.0</td>
<td>235 (38%)</td>
<td>3025 (57%)</td>
</tr>
<tr>
<td>&gt; 7.0</td>
<td>379 (62%)</td>
<td>2318 (43%)</td>
</tr>
</tbody>
</table>
Primary prevention of CAD in diabetic patients
Evidence from lipid lowering drug trials

1. Direct evidence
2. Subgroup analyses of RCTs
3. In progress studies
3. In progress studies

• **FIELD- Fenofibrate Intervention and Event Lowering in Diabetes**
  Is examining the effects of micronized fenofibrate on total and fatal CAD events in men and women with Type 2 diabetes, some of whom are known to have coronary disease.

• **CARDS - Collaborative Atorvastatin Diabetes Study**
  Is examining the effects of atorvastatin treatment versus placebo in 2,120 patients with Type 2 diabetes and no established cardiovascular disease.

• **LDS Lipids in Diabetes Study**
  Stopped following withdrawal of cerivastatin
CLINICAL QUESTIONS
2. What is your drug choice for managing dyslipidemia?

1. Resine
2. Statin
3. Fibrate
4. Nicotinic acid
Position statement

Management of Dyslipidemia in Adults With Diabetes

American Diabetes Association, 2002
<table>
<thead>
<tr>
<th>Table 3—Order of priorities for treatment of diabetic dyslipidemia in adults*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. LDL cholesterol lowering*</td>
</tr>
<tr>
<td>First choice</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitor (statin)</td>
</tr>
<tr>
<td>Second choice</td>
</tr>
<tr>
<td>Bile acid binding resin (resin) or fenofibrate</td>
</tr>
<tr>
<td>II. HDL cholesterol raising</td>
</tr>
<tr>
<td>Behavioral interventions such as weight loss, increased physical activity, and smoking cessation may be useful</td>
</tr>
<tr>
<td>Difficult except with nicotinic acid, which should be used with caution, or fibrates</td>
</tr>
<tr>
<td>III. Triglyceride lowering</td>
</tr>
<tr>
<td>Glycemic control first priority</td>
</tr>
<tr>
<td>Fibric acid derivative (gemfibrozil, fenofibrate)</td>
</tr>
<tr>
<td>Statins are moderately effective at high dose in hypertriglyceridemic subjects who also have high LDL cholesterol</td>
</tr>
<tr>
<td>IV. Combined hyperlipidemia</td>
</tr>
<tr>
<td>First choice</td>
</tr>
<tr>
<td>Improved glycemic control plus high-dose statin</td>
</tr>
<tr>
<td>Second choice</td>
</tr>
<tr>
<td>Improved glycemic control plus statin† plus fibric acid derivative† (gemfibrozil, fenofibrate)</td>
</tr>
<tr>
<td>Third choice</td>
</tr>
<tr>
<td>Improved glycemic control plus resin plus fibric acid derivative (gemfibrozil, fenofibrate)</td>
</tr>
<tr>
<td>Improved glycemic control plus statin† plus nicotinic acid† (glycemic control must be monitored carefully)</td>
</tr>
</tbody>
</table>

*Decision for treatment of high LDL before elevated triglyceride is based on clinical trial data indicating safety as well as efficacy of the available agents. †The combination of statins with nicotinic acid and especially with gemfibrozil or fenofibrate may carry an increased risk of myositis. See text for recommendations for patients with triglyceride levels >400 mg/dl.
CLINICAL QUESTIONS
3. What statin do you prescribe?

1. Atorvastatin
2. Fluvastatin
3. Lovastatin
4. Pravastatin
5. Simvastatin
Therapeutic decision

• We prescribe Atorvastatin 20 mg/die, then increased to 40 mg/die after 3 months

• The patient were advised to monitor CPK, GOT, GPT after one month, and thereafter, every six months
Pedersen T, Gaw A

Statins
Similarities and differences

• The number of statins available to physicians continues to grow, leading to the question: Are all statins alike?

• Comparisons of side effects and safety profiles and the dose-response relationship among the different drugs show similar results.

• On the other hand, the molecular structures of the newer statins are not similar and could have an effect on the mechanism of action of the compounds.

• Differences in metabolism also suggest the possibility of serious drug-drug interactions.

### Statins

What evidence about relevant end-points?

<table>
<thead>
<tr>
<th>Statin</th>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>HPS</td>
<td>4S, HPS</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>WOSCOPS</td>
<td>CARE, LIPID</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>AFCAPS/TexCAPS</td>
<td>-</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Psaty BM, Weiss NS, Furberg CD, et al.

Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease

JAMA 1999;282:786-90
Should new drugs be used without outcome data?
Implications of ALLHAT and ELITE II

Arch Intern Med 2001;161:511-12
Surrogate End Points in Clinical Trials
Are We Being Misled?

Disease

Intervention

Surrogate End Point

True Clinical Outcome

Sotiriou CG, Cheng JW

Beneficial effects of statins in coronary artery disease
Beyond lowering cholesterol

Ann Pharmacother 2000;34:1432-9
• Beneficial effects on vessel endothelial tissue

• Decreased low-density lipoprotein oxidation and inflammation

• Ability to stabilize atherosclerotic plaques and perhaps promote regression

• Proliferative effects on smooth-muscle growths

• Antithrombotic effects by inhibiting platelet aggregation and stimulation of fibrinolytic factors

• Improvement of blood viscosity and flow

Clinical scenario (5)

After six months

- Blood pressure: 140/88 mmHg
- Renal and liver function: normal
- Lipid profile

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<th>Baseline</th>
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<th>12 months</th>
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<tr>
<td>Serum cholesterol</td>
<td>260</td>
<td>240</td>
<td>190</td>
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<td>Serum triglycerides</td>
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CLINICAL QUESTIONS
4. Considering the actual lipid profile in a patient with high cardiovascular risk, what is your therapeutic choice?

1. Higher doses of statin
2. Starting resine
3. Starting fibrate
4. Starting nicotinic acid
5. No further drug prescription
Figure 2. Progression of Drug Therapy in Primary Prevention

- Initiate LDL-Lowering Drug Therapy
- If LDL Goal Not Achieved, Intensify LDL-Lowering Drug Therapy
- If LDL Goal Not Achieved, Intensify Drug Therapy or Refer to a Lipid Specialist
- Every 4-6 Months
- Monitor Response and Adherence to Therapy

- Start Statin or Bile Acid Sequestrant or Nicotinic Acid
- Consider Higher Dose of Statin or Add Bile Acid Sequestrant or Nicotinic Acid
- If LDL Goal Achieved, Treat Other Lipid Risk Factors

LDL indicates low-density lipoprotein.
Absolute benefits of lowering LDL cholesterol concentrations appear to depend chiefly on the absolute risks of coronary heart disease (rather than on cholesterol concentrations)

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial

Heart Protection Study Collaborative Group*
Lack of evidence for LDL cholesterol threshold

• HPS has demonstrated unequivocally that lowering LDL cholesterol from below 116 to below 77 mg/dL reduces vascular disease risk by about one-quarter.

• Current guidelines may inadvertently lead to substantial under-treatment of high-risk patients who present with LDL cholesterol concentrations below, or close to, particular targets (such as 100 mg/dL in the ATP III guidelines)
Therapeutic decision

• We add fenofibrate 200 mg, with caution for the possible untoward effects

• Monitor CPK, GOT, GPT after one month and thereafter every 2-3 months

• Optimize blood pressure control
Clinical scenario (6)

After three months

- Blood pressure: 138/80 mmHg
- CPK, COT, GPT normal
- Lipid profile

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