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 150 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

Diagnosis
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>
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<td>186</td>
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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)

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
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

Dont’ forget!

<table>
<thead>
<tr>
<th>Table 2—Treatmenet choices based on LDL cholesterol level in adults with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Serum Cholesterol Level</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>100 mg/dL or lower</td>
</tr>
<tr>
<td>100-129 mg/dL</td>
</tr>
<tr>
<td>130-159 mg/dL</td>
</tr>
<tr>
<td>160-189 mg/dL</td>
</tr>
<tr>
<td>190-229 mg/dL</td>
</tr>
<tr>
<td>230 mg/dL or higher</td>
</tr>
</tbody>
</table>

Table 2—Treatment choices based on LDL cholesterol level in adults with diabetes.

- This table is a standard recommendation for treatment of cholesterol levels in adults with diabetes.
- The table is divided into categories based on initial serum cholesterol level and LDL cholesterol goal.
- The maximum LDL cholesterol goal is also specified for each category.
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.

- 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 Chart.
- Lipid lowering drug therapy should be considered at a lower risk threshold in diabetics with nephropathy.

| Risk Category | LDL Cholesterol (mg/dL) Goal if Therapy in Primary Prevention
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (10 year CHD risk &lt;10%)</td>
<td>100</td>
</tr>
<tr>
<td>Intermediate 1 risk (10 year CHD risk 10-20%)</td>
<td>130</td>
</tr>
<tr>
<td>20-30%</td>
<td>160</td>
</tr>
<tr>
<td>High risk (10 year CHD risk &gt;30%)</td>
<td>190</td>
</tr>
<tr>
<td>Very high risk (10 year CHD risk &gt;50%)</td>
<td>220</td>
</tr>
</tbody>
</table>

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**

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

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

<table>
<thead>
<tr>
<th>Study</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 1998</td>
<td>Bezaflurate</td>
<td>MI or new ischemic changes on ECG</td>
<td>3</td>
<td>5/64</td>
<td>16/64</td>
<td>6 (5 to 20)</td>
</tr>
<tr>
<td>DAIS 2001</td>
<td>Micronized Fenofibrate</td>
<td>Death or MI</td>
<td>3.8</td>
<td>19/207</td>
<td>21/111</td>
<td>NS</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
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 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.

Subgroup analysis

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

2. Subgroup analysis of RCTs

Until 2002

<table>
<thead>
<tr>
<th>RCT</th>
<th>Drug</th>
<th>Outcome</th>
<th>Years</th>
<th>Events/pts</th>
<th>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>60/558*</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

Astrological birth sign | Vascular death by 1 month | p |
------------------------|---------------------------|---|
Libra or Gemini         | 150 (11.3%)               | 0.5 |
Aries or Leo            | 147 (10.3%)               |    |
|                        | 884 (9.0%)                |    |
|                        | 899 (12.1%)               |    |

Table 3: Unreliability of "data-dependent" subgroup analyses: ISHIS-2 trial of aspirin among over 17 000 patients with suspected acute myocardial infarction

1. Subgroup analyses of RCTs

THF LANCET • Vol 300 • July 6, 2002 • www.thelancet.com

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

Henderson SR et al. "MRC/BHF Heart Protection Study Collaborative Group"
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

Table 1. Baseline characteristics of patients with diabetes enrolled in the LDL-SEP from intervention trials

<table>
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<tr>
<th>Parameter</th>
<th>Simvastatin-allocated</th>
<th>Placebo-allocated</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. prior CAD</td>
<td>79/87 (18-76)</td>
<td>71/83 (27-82)</td>
</tr>
<tr>
<td>+ Diabetes Mellitus</td>
<td>12/19 (10-76)</td>
<td>15/21 (27-84)</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>122/126 (21-78)</td>
<td>162/166 (20-74)</td>
</tr>
<tr>
<td>+ Diabetes Mellitus</td>
<td>27/28 (13-68)</td>
<td>30/31 (13-68)</td>
</tr>
<tr>
<td>Subtotal: no CHD</td>
<td>574/575 (50-15)</td>
<td>744/575 (20-60)</td>
</tr>
</tbody>
</table>

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

but....

CLAUSAL QUESTIONS

2. What is your drug choice for managing dyslipidemia?

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

Management of Dyslipidemia in Adults With Diabetes

American Diabetes Association, 2002

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.

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### Statins

What evidence about relevant end-points?

<table>
<thead>
<tr>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
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<tbody>
<tr>
<td>Simvastatin</td>
<td>HPS</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>WOSCOPS, CARE, LIPID</td>
</tr>
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<td>Lovastatin</td>
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<td>Cerivastatin</td>
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</tr>
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<td>Atorvastatin</td>
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**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*

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**Kaplan NM**

Should new drugs be used without outcome data?

Implications of ALLHAT and ELITE II

*Arch Intern Med 2001;161:511-12*

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**Surrogate End Points in Clinical Trials**

Are We Being Misled?

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**Soliriou 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 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

Absolute benefits of lowering LDL cholesterol concentrations appear to depend chiefly on the absolute risks of coronary heart disease (rather than on cholesterol concentrations)

ATP III. JAMA, 2001

Armitage J. et al. Heart 2003

Clinical scenario (5)

After six months
• Blood pressure: 140/88 mmHg
• Renal and liver function: normal
• Lipid profile

<table>
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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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