2nd AME Italian Meeting
Associazione Medici Endocrinologi
Joint Meeting with AACE
American Association of Clinical Endocrinologists
Reggio Emilia, Italy - November 8-10, 2002

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

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

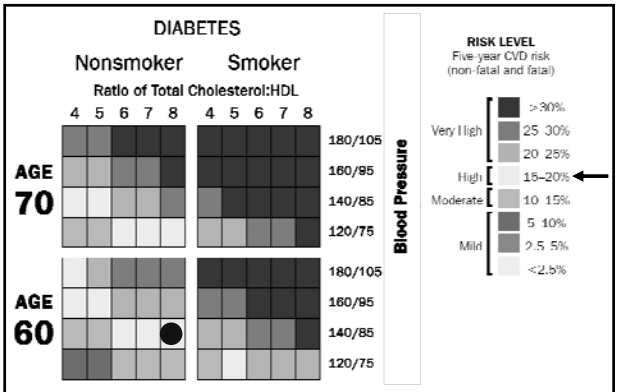
	Baseline	6 months
Serum cholesterol	260	240
Serum triglycerides	320	260
HDL cholesterol	22	25
LDL cholesterol	186	163

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)

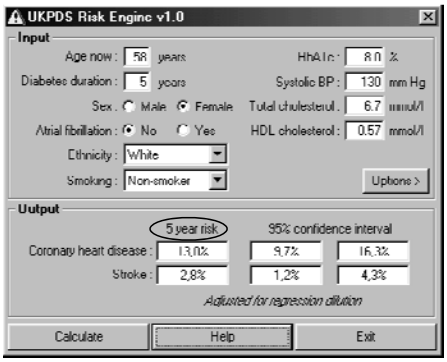


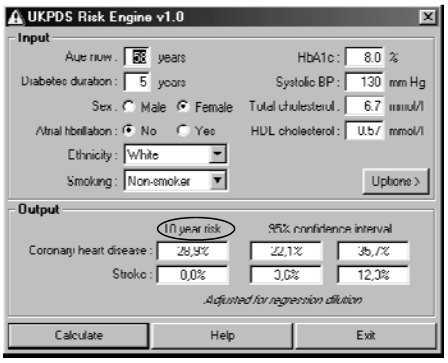
Adler AI, Stratten IM, Holman RR, et al.

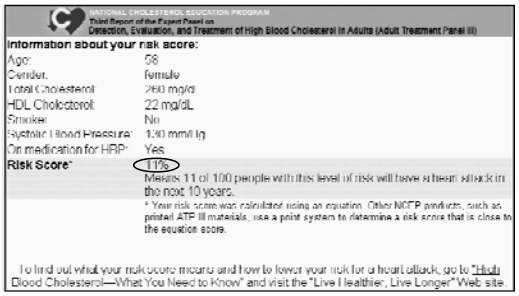
The UKPDS Risk Engine

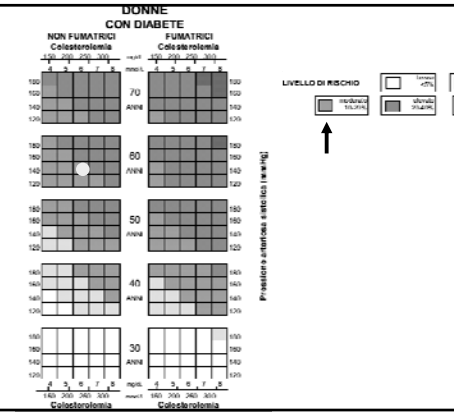
A model for the risk of coronary heart disease in type 2 diabetes

Clinical Science 2001;101:671-679









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

American Diabetes Association.
Cure • Care • Commitment™

Diabetes Care

Table 2—*Treatment decisions based on LDL cholesterol level in adults with diabetes*

	Medical nutrition therapy		Drug therapy	
	Initiation level	LDL goal	Initiation level	LDL goal
With CHD, PVD, or CVD	≥100	<100	≥100	<100
Without CHD, PVD, and CVD	≥100	<100	≥130*	<100

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 fibric acid such as fenofibrate may be used in these patients. MNT should be attempted before starting pharmacological therapy. PVD, peripheral vascular disease.

National Heart, Lung, and Blood Institute

NATIONAL CHOLESTEROL EDUCATION PROGRAM

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

National Heart, Lung, and Blood Institute

NATIONAL CHOLESTEROL EDUCATION PROGRAM

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

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

*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, eg, 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.

SIGN

Scottish Intercollegiate Guidelines Network

- 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

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

Haffner SM, Lehto S, Ronnemaa T, et al.

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

N Engl J Med 1998;339:229-234

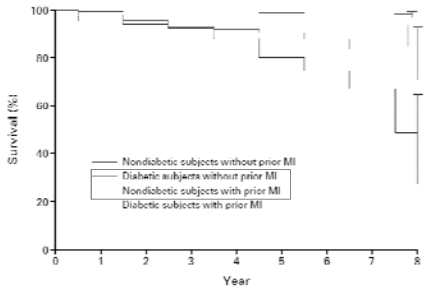


Figure 1. Kaplan–Meier Estimates of the Probability of Death from Coronary Heart Disease in 1059 Subjects with Type 2 Diabetes and 1379 Nondiabetic Subjects with and without Prior Myocardial Infarction. MI denotes myocardial infarction. I bars indicate 95 percent confidence intervals.

Haffner SM, et al. N Engl J Med 1998

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

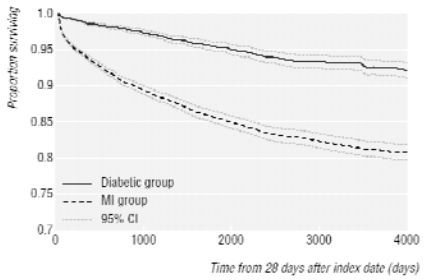


Fig 2 Kaplan-Meier survival curve showing time to death from cardiovascular causes in patients with newly diagnosed type 2 diabetes and patients who had just had a myocardial infarction (MI)

Evans JMM. BMJ, 2002

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

RCT	Drug	Outcome	Years	Event/pts	Event/pts	NNT
SENDCAP 1998	Bezafibrate	MI or new ischaemic changes on ECG	3	5/64	16/64	6 (5 to 20)
DAIS 2001	Micronized Fenofibrate	Death or MI	3.8	15/207	21/111	NS

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

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

*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
	Aspirin	Placebo	
Libra or Gemini	150 (11·1%)	147 (10·2%)	0·5
All other signs	654 (9·0%)	869 (12·1%)	<0·0001
Any birth sign	804 (9·4%)	1016 (11·8%)	<0·0001

Table 3: **Unreliability of "data-dependent" subgroup analyses: ISIS-2 trial of aspirin among over 17 000 patients with suspected acute myocardial infarction[23]**

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

1. Subgroup analyses of RCTs

THE LANCET • Vol 360 • July 6, 2002 • www.thelancet.com

Articles

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	Placebo-allocated
No prior CHD		
+ Cerebrovascular	172/922 (18·7%)	212/898 (23·6%)
+ Peripheral vascular	327/1325 (24·7%)	420/1376 (30·5%)
+ Diabetes mellitus	276/2006 (13·8%)	367/1976 (18·6%)
Subtotal: no CHD	**574/3575 (16·1%)**	**744/3575 (20·8%)**

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

but….

Table 1 Baseline characteristics of patients with diabetes mellitus in the MRC/BHF heart protection study

Characteristic at entry	Type 1 (n=613)		Type 2 (n=5848)	
Disease history				
Myocardial infarction	30	(5%)	1095	(20%)
Other CHD	31	(5%)	822	(15%)
Other cardiovascular	124	(20%)	918	(18%)
No cardiovascular	430	(70%)	2883	(56%)
Treated hypertension	118	(19%)	2279	(43%)
Duration of diabetes (years)	28.6	(0.5)	9.3	(0.1)
Age (years)	52.6	(0.3)	63.2	(0.1)
< 65	564	(92%)	3082	(58%)
≥ 65	51	(8%)	2266	(42%)
Total cholesterol (mmol/l)	5.52	(0.04)	5.68	(0.01)
< 5.5	315	(51%)	2464	(46%)
≥ 5.5 & < 7.0	257	(47%)	2349	(44%)
≥ 7.0	43	(7%)	535	(10%)
LDL cholesterol (mmol/l)*	3.01	(0.03)	3.24	(0.01)
< 3.0	330	(54%)	2131	(40%)
≥ 3.0 & < 3.5	113	(18%)	1306	(24%)
≥ 3.5	172	(28%)	1911	(36%)
HDL cholesterol (mmol/l)*	1.40	(0.02)	1.02	(0.00)
≤ 1.0	96	(16%)	3073	(57%)
> 1.0	519	(84%)	2335	(43%)
Triglycerides (mmol/l)	1.24	(0.03)	2.38	(0.02)
< 2.0	526	(86%)	2690	(50%)
≥ 2.0	89	(14%)	2658	(50%)
HbA_{1c} (%)†	7.90	(0.09)	7.04	(0.03)
< 7.0	235	(38%)	3025	(57%)
≥ 7.0	379	(62%)	2318	(43%)

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 3—*Order of priorities for treatment of diabetic dyslipidemia in adults**

I. LDL cholesterol lowering*
- First choice
  - HMG CoA reductase inhibitor (statin)
- Second choice
  - Bile acid binding resin (resin) or fenofibrate

II. HDL cholesterol raising
- Behavioral interventions such as weight loss, increased physical activity, and smoking cessation may be useful
- Difficult except with nicotinic acid, which should be used with caution, or fibrates

III. Triglyceride lowering
- Glycemic control first priority
- Fibric acid derivative (gemfibrozil, fenofibrate)
- Statins are moderately effective at high dose in hypertriglyceridemic subjects who also have high LDL cholesterol

→ IV. Combined hyperlipidemia
- First choice
  - Improved glycemic control plus high-dose statin
- Second choice
  - Improved glycemic control plus statin† plus fibric acid derivative† (gemfibrozil, fenofibrate)
- Third choice
  - Improved glycemic control plus resin plus fibric acid derivative (gemfibrozil, fenofibrate)
  - Improved glycemic control plus statin† plus nicotinic acid‡ (glycemic control must be monitored carefully)

*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 yo 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

Am J Manag Care 2001;7(5 Suppl):S132-7

• 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

Pedersen T, et al. Am J Manag Care 2001

Statins
What evidence about relevant end-points?

	Primary Prevention	Secondary Prevention
Simvastatin	HPS	4S, HPS
Pravastatin	WOSCOPS	CARE, LIPID
Lovastatin	AFCAPS/TexCAPS	-
Cerivastatin	-	-
Fluvastatin	-	-
Atorvastatin	-	-

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

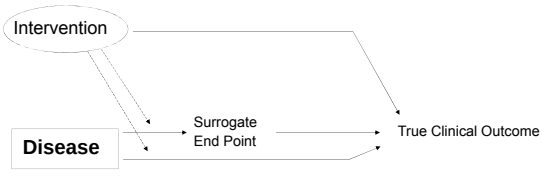
JAMA 1999;282:786-90

Kaplan NM

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?



Fleming T, et al. Ann Intern Med 1996

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

Sotiriou CG, et al. Ann Pharmacother, 2000

Clinical scenario (5)

After six months

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

	Baseline	6 months	12 months
Serum cholesterol	260	240	190
Serum triglycerides	320	260	250
HDL cholesterol	22	25	28
LDL cholesterol	186	163	110

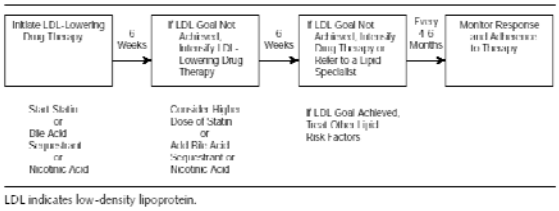
CLINICAL QUESTIONS

?

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



LDL indicates low-density lipoprotein.

ATP III. JAMA, 2001

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

Armitage J, et al. Heart 2000

THE LANCET • Vol 360 • July 6, 2002 • www.thelancet.com

ARTICLES

Articles

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

	Baseline	6 months	12 months	15 months
Serum cholesterol	260	240	190	180
Serum triglycerides	320	260	250	184
HDL cholesterol	22	25	28	35
LDL cholesterol	186	163	110	110