Clin Invest Arterioscl. 2010;**22(Supl 2)**:48-51

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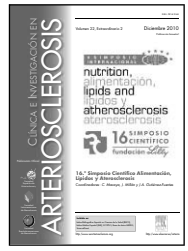

16.º SIMPOSIO CIENTÍFICO ALIMENTACIÓN, LÍPIDOS Y ATEROSCLEROSIS

Efficacy and benefits of lipid-lowering drug therapy. The new European guidelines for cardiovascular disease prevention

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Benefits and safety of lipid-lowering drugs that are commercially available

In most European countries the current armamentarium of lipid-lowering drugs includes statins, fibrates, resins, nicotinic acid and ezetimibe.

All of these drug classes with the exception of ezetimibe have been shown in trials to reduce myocardial infarction and coronary death.

The most convincing evidence from clinical end point trials has been obtained with the most potent of the lipid-lowering drugs- the statins.

In a meta-analysis of data from 90056 participants in 14 trials of statins the Cholesterol Treatment trialists' collaborators reported that for 1 mmol/L LDL cholesterol reduction the risk for a major coronary event was reduced by 23%.

Also important is that these results are very homogeneous if one looks at more specific endpoints or at a more general picture which is all cause mortality: all cause mortality was reduced by 12% for 1 mmol/L LDL cholesterol reduction. Non fatal myocardial infarction was reduced by 26%, coronary death by 19%; 1 mmol/L LDL cholesterol reduction was accompanied by 25% less coronary bypass surgery and by 21% less PTCA. Stroke was reduced by 17%.

Reassuring is that both cancer deaths and cancer incidence were unrelated to LDL cholesterol reduction.

The proportional reduction in major coronary or vascular event rates per 1 mmol/L LDL cholesterol reduction was very similar in all of the subgroups examined: previous coronary heart disease (CHD), age, gender, treatment of hypertension, history of diabetes, diastolic blood pressure and subgroups by lipid levels.

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In all theses subclasses 1 mmol/L LDL cholesterol reduction was associated with 20 to 25% reduction in vascular or coronary events. The benefits were significant within the first year but were greater in subsequent years.

The efficacy and safety of statins may be well documented but important questions still remain unanswered.

A. The treatment goals that are used in the guidelines are arbitrary; data are missing from studies comparing different treatment goals. There are only a few studies comparing different doses of statins:

—In the TNT study treatment with 80 mg atorvastatin reduced major cardiovascular (CV) event rate by —22% compared to the group treated with 10mg atorvastatin[2].
—In the PROVE-IT study 40 mg pravastatin was inferior to 80 mg atorvastatin[3] but the IDEAL study failed to demonstrate a significant difference in the outcome after treatment with 80 mg atorvastatin and 20 mg simvastatin[4].

Thus studies comparing different treatment goals are needed. In the meantime one should aim to achieve substantial absolute reductions in LDL cholesterol since the risk reductions are proportional to the absolute LDL cholesterol reduction. Target levels should be used as management tools in the patient-doctor communication.

B. There are still major gaps in our knowledge concerning other lipid-lowering drugs: resins, fibrates and nicotinic acid reduce cholesterol but data from studies with hard endpoints are limited. Hard endpoint studies are needed comparing these drugs in combination with statins compared to statins alone. We also need ezetimibe studies with hard endpoints preferably comparing ezetimibe in combination with a statin compared to statin alone as now in progress in the IMPROVE IT trial[5].

How effective are lipid-lowering drugs in preventing cardiovascular disease (CVD)?

As already mentioned the Cholesterol Treatment trialists' collaborators found in a meta-analysis from 14 trials of statins that for each mmol/L lowering of LDL cholesterol statin therapy was effective in reducing the risk of major vascular events by 21%[1].

But despite this, the residual risk of a major vascular event remained high: 14% of the patients allocated to statins experienced a cardiovascular event compared to 18% in the placebo group; this means a residual risk of 78% of what was experienced in the placebo group.

One may argue that in some of these trials LDL cholesterol was not sufficiently reduced.

But in the Treatment to New Targets trial (TNT) patients taking 80 mg of atorvastatin reached on average a LDL cholesterol of 77 mg/dL (1.99 mmol/L) and were compared with patients taking 10 mg of atorvastatin reaching on average an LDL cholesterol of 101mg/dL (2.61 mmol/L). Those on the higher dose had a 28% event rate compared to 33% in the lower dose group, a 22% relative risk reduction. But this also means that 70% of all expected events were not avoided in the high dose group despite a significant improvement in LDL cholesterol reduction[2].

Why do patients on an aggressive lipid lowering therapy continue to develop CV events? Different explanations can be put forward.

Could it be that the strategy is too aggressive causing adverse events and therefore drop-out, non-compliance and less effectiveness?

Or could it be that the strategy is not aggressive enough, that one should aim at even lower LDL cholesterol levels?

Another straightforward explanation is based on the knowledge that CVD are multifactorial in origin; focusing on only one risk factor even aggressively may be insufficient; the European guidelines emphasize since more than 15 yrs that one should look at the total CV risk and adapt the intensity of the preventive actions in accordance with the total CV risk of the individual.

In several trials it was shown that higher vascular event rates were seen in patients with additional modifiable risk factors:

For instance in the Heart Protection Study (HPS) simvastatin was effective in all subgroups by smoking status but smokers on simvastatin had a higher CV event rate than the never smokers on placebo: 22.8 versus 20.6%[3]. But never smokers on simvastatin still had an event rate of 16% which means a residual risk of more than 50% of what was observed in the smokers on placebo.

In the same HPS, patients with CAD and diabetes who were receiving simvastatin had an event rate of 33% which is much more than the 26% in patients with CAD on placebo but without diabetes[7].

Different options are open for explaining this observation. The most obvious one is to consider all modifiable risk factors not only the lipids. If for instance the patients from HPS with CAD and diabetes but with a HbA1c of < 7% are selected the residual risk in these patients is equal to patients free of diabetes suggesting that a good control of the diabetes makes all the difference as to the enhanced residual risk in patients with diabetes.

Lipid-lowering therapies within the European Guidelines on CVD prevention in clinical practice

The most recent update of the European Guidelines on CVD prevention in clinical practice was produced by the Fourth Joint Task Force and published in 2007 by a consortium of 9 European Societies[8]. Most important is that lipid management should not be considered in isolation but as an integral part of total CV risk management.

The overall objectives of CVD prevention are to assist those at low risk of CVD to maintain this state lifelong, and to help those at increased total CVD risk to reduce it.

This means the characteristics of people who tend to stay healthy should be achieved and these are:

—No smoking.
—Healthy food choices.
—Physical activity: 30 min of moderate activity a day.
—BMI < 25 kg/m? and avoidance of central obesity.
—Blood pressure < 140/90 mmHg.
—Total cholesterol < 5 mmol/L (–190 mg/dL).
—LDL cholesterol < 3 mmol/L (–115 mg/dL).
—Blood glucose < 6 mmol/L (–110 mg/dL).

In addition, more rigorous risk factor control should be aimed at in high risk subjects, especially in patients with established CVD or diabetes. In them we should aim at:

—Blood pressure under 130/80 mmHg if feasible.
—Total cholesterol < 4.5 mmol/L (–175 mg/dL) with an option of < 4 mmol/L (–155 mg/dL) if feasible.
—LDL cholesterol < 2.5 mmol/L (–100 mg/dL) with an option of < 2 mmol/L (–80 mg/dL) if feasible.
—Fasting blood glucose < 6 mmol/L (–110mg/dL) and HbA1c < 6.5% if feasible.
—And furthermore cardioprotective drug therapy should be considered in high risk subjects especially in those with established atherosclerotic CVD.

How to identify those at high risk?

Some are easy to identify: patients with established CVD, with type 2 diabetes, or type 1 diabetes and microalbuminuria or patients with severe hypercholesterolaemia are at high risk.

But the majority of high risk patients in society are among the asymptomatic population. Their identification needs special risk estimation models such as the SCORE model that was developed for Europe[9].

SCORE has the great advantage that it can be calibrated according to local national figures resulting in a total CV risk model that fits closely to the target population.

With the SCORE charts comes a table with qualifiers emphasizing that in front of a given patient the clinician

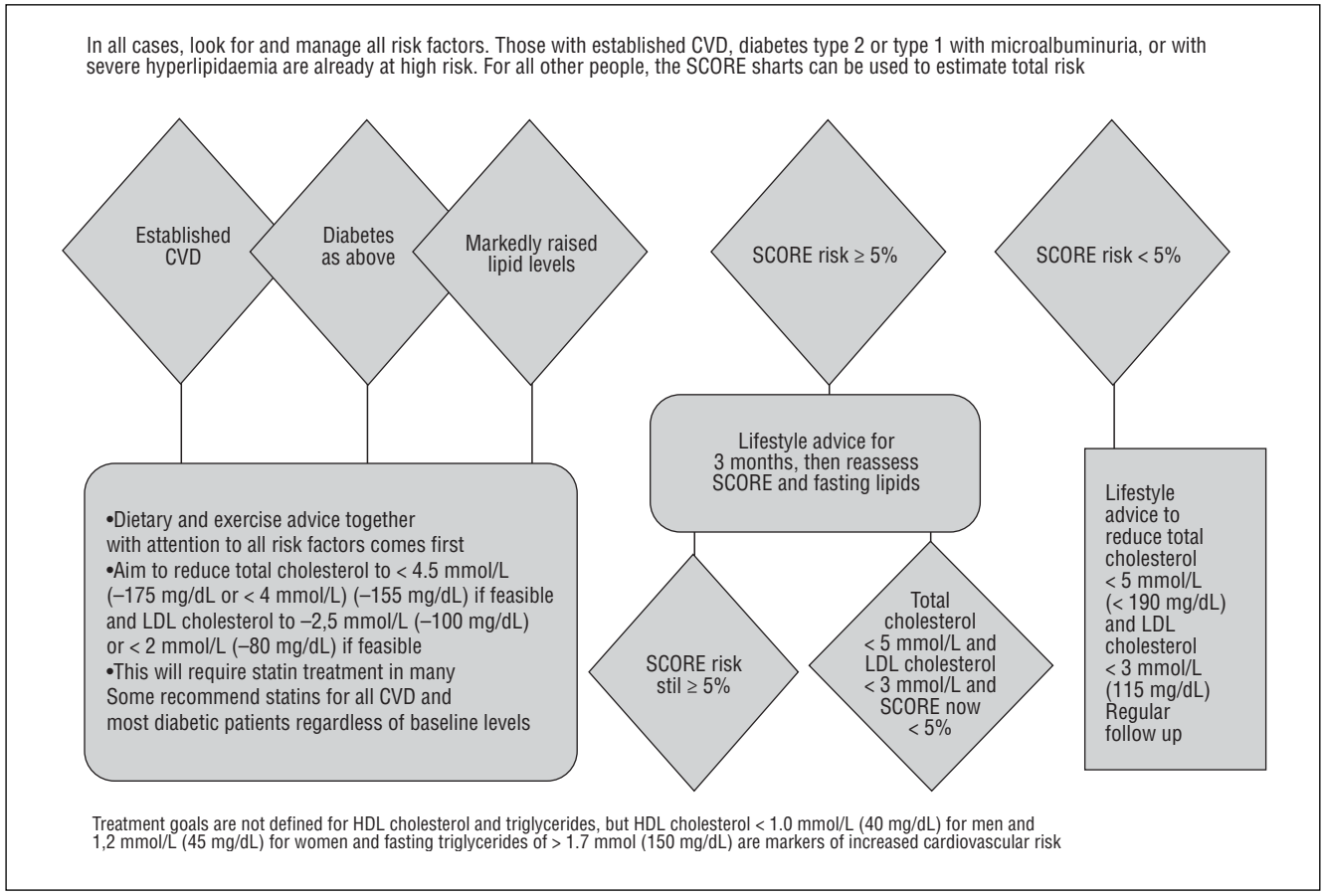

Figure 1 Lipid management.

can even improve risk prediction by considering also other CV risk factors that were not included in the SCORE model and that increase the total risk even more:

—In sedentary or obese subjects, especially in those with central obesity.
—In those with a strong family history of premature CVD.
—In the socially deprived.
—In those with low HDL cholesterol or high triglycerides.
—In asymptomatic subjects with evidence of pre-clinical atherosclerosis.

Regarding lipid management the recent guidelines provide an algorhythm (Fig. 1).

—In asymptomatic subjects at low total risk one should do everything to keep total CV risk as low as possible for as long as possible.
—In those at higher risk one should try to get at goal for total and LDL cholesterol with non-pharmacological interventions particularly related to nutrition, exercise and avoidance of tobacco. When this is insufficient and certainly in those at highest risk drug therapies have to be considered aiming at a total cholesterol of < 4.5 mmol/L (–175 mg/dL) or < 4 mmol/L (–155 mg/dL) if feasible and at a LDL cholesterol of < 2.5 mmol/L (–100 mg/dL) or < 2 mmol/L (–80 mg/dL) if feasible.

This will require statin treatment in many of these subjects at highest total CV risk.

Treatment goals are not defined for HDL cholesterol and triglycerides, but HDL cholesterol < 1.0 mmol/L (40 mg/dL) for men and < 1.2 mmol/L (45 mg/dL) for women and fasting triglycerides of > 1.7 mmol/L (150 mg/dL) are markers of increased cardiovascular risk.

Conclusion

The approach towards CVD prevention needs a comprehensive multifactorial strategy focusing on all modifiable risk factors.

Preventive actions should be guided in accordance to the total CVD risk level:

—Those at highest risk should receive intensive lifestyle intervention + drug therapy in a majority.
—Those at high risk should receive intensive lifestyle intervention + drug therapy when appropriate.
—Those at mild or moderate risk should receive lifestyle intervention targeting at a more optimal risk profile.
—Those at low risk should be advised to keep it as low as possible.

The problem with CVD prevention is not the need for more personalized treatment but the failure to act in those who have the potential to benefit.

Conflict of interest

The Department of Public Health chaired by G. De Backer until 2009 has received research grants in the past from Solvay, Astra-Zeneca, MSD/SP, and Pfizer.

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