

## Ezetimibe: what role in the light of recent guidelines?

### Summary

The reduction of total and LDL-cholesterol to levels established in current National Cholesterol Education Program (NCEP) guidelines provides 30-40% of coronary risk reduction. Unfortunately, many patients receiving statin therapy do not reach LDL-cholesterol goals with their current dosage, so many patients do not benefit of potential risk reduction. Ezetimibe is the first agent of a novel class of selective cholesterol absorption inhibitors. Its favorable pharmacokinetic profile allows it to be administered once daily and to be given in conjunction with statins. Many clinical trials showed that co-administration of ezetimibe with a statin is more effective than statin monotherapy in lowering LDL-cholesterol and improving other lipid parameters (HDL, CRP TG, TC:HDL ratio), allowing a greater percentage of patients to achieve lipid goals established in NCEP guidelines. This paper reviews the goals of lipid lowering therapy, the magnitude of the treatment gap with guidelines, the pharmacological options available and the place of ezetimibe in the light of current guidelines.

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### Maurizio Averna<sup>1</sup>, Enzo Manzato<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, University of Palermo, Italy

<sup>2</sup>Department of Medical and Surgical Sciences, University of Padova, Padova, Italy

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**guidelines**

The impact of statins on the treatment of lipid metabolism alterations has been compared by some authors to that of penicillin on curing infections<sup>1</sup>. The similarity mainly concerns the predictability of the clinical response that characterizes HMGCoA-reductase inhibitors, since they induce the expected response in nearly all patients if suitably administered. Although the lipid lowering effects are quickly visible after the first few weeks, the clinical benefits of statins can only be measured after a relatively long treatment period: the majority of clinical trials and the various meta-analyses suggest that substantial reductions in the clinical end points can only be measured after three years of treatment<sup>2-4</sup>.

Thanks to their various pharmacological properties (pleiotropy), statins have monopolized the treatment of dyslipida-

emia for nearly two decades, and have changed the scene of lipid metabolism pathophysiology and the study of vascular risk. As a consequence of this line of research, no new lipid lowering drugs have been introduced into clinical practice since the mid 1980s. The introduction of ezetimibe is therefore the first pharmacological innovation in the treatment of dyslipidaemia after nearly twenty years. At present, the true importance of this new class of cholesterol lowering drugs is not completely predictable. In this review, we examine the role of ezetimibe on the present clinical scene and in the light of the most recent guidelines.

### The clinical scene

The clinical context in which the ezetimibe/simvastatin combination has been introduced is one of the most flexible areas



### Maurizio Averna

Department of Internal Medicine,  
 University of Palermo,  
 Via del Vespro 141,  
 90127 Palermo, Italy

of cardiovascular research, with many large trials that have been already completed and several others still under way. Since 1994, the year the first big trial with statins was published (Scandinavian Simvastatin Survival Study-4S), these trials have provided an enormous quantity of clinical data, which confirm many of the working assumptions they were designed to<sup>5</sup>. In May 2001, the National Cholesterol Education Program (NCEP) released its Third Executive Summary on the basis of the results of a few fundamental trials and a few sub-analyses. This document equated the risk of coronary heart disease to that of other diseases with a high cardiovascular impact, such as diabetes and peripheral vascular disease, thus for the first time virtually creating a *continuum* between primary and secondary prevention<sup>6</sup>.

### The new therapeutic aims

As a consequence of this assumption, a "desirable serum cholesterol-LDL value" <100 mg/dl, originally proposed *only* for patients with previously diagnosed coronary heart disease, was extended to a rather larger number of "high risk patients". These not only included all patients with coronary heart disease, but also patients with multiple risk factors (absolute risk >20% at 10 years), diabetics and all those with other atherosclerotic vascular diseases (carotid arteries, lower limbs and abdominal aorta).

In July 2004, the NCEP released a new version of the previous text: the new document defined a subpopulation at *very high coronary risk*, in addition to the high risk group, for which even lower LDL values (LDL <70 mg/dl) than those normally

envisaged for secondary prevention (LDL <100 mg/dl) might be desirable<sup>7</sup>. This new approach stemmed from the results of some clinical trials (PROVE-IT, TNT) in which the subpopulation at very high risk, i.e. estimated as rather greater than >20% at 10 years (AMI plus diabetes, acute coronary syndromes, diffuse coronary disease), benefited from aggressive lipid lowering treatment (LDL goal  $\approx$ 75 mg/dl) in comparison with counterparts who received blander treatments (goal LDL <100 mg/dl)<sup>8-11</sup>.

This hypothesis was recently challenged by the results of the IDEAL trial, in which patients with previously diagnosed AMI were treated with atorvastatin (80 mg/day) or simvastatin (20 mg/day)<sup>12</sup>. In this trial, despite a difference in LDL concentrations of about 20 mg/dl in the two treatment groups (81 *vs.* 104 mg/dl), no significant differences were recorded in the prefixed end points.

At present therefore, the advantages of aggressive treatments over milder treatments is still

controversial and should be substantiated with further trials to see if there is an LDL level below which further decreases still have a favourable cost-effectiveness ratio. In the absence of new consensus documents, and therefore considering the document issued by the NCEP in 2004 as still valid, the lipid goals stratified by risk group may be summarized as shown in table 1.

### Guidelines and clinical practice: the gap

As things stand, it can therefore be stated that a suitably decrease of LDL fraction is still the only therapeutic goal which has given satisfactory clinical responses and which is shared by the scientific community. Until we are able to act on other targets (HDL fraction, triglycerides, Lp(a), etc.), action on LDLs is therefore still priority in all consensus documents. It follows that any drug which contributes towards a further reduction of LDLs contributes towards a further decrease of cardiovascular risk.

**Table 1.** Lipid lowering treatment goals fixed by the NCEP III 2004 guidelines on the basis of absolute risk. (Data from Grundy SM *et al.* 2004<sup>7</sup>).

Risk group/type of patient	LDL goal
Extremely high risk (much greater than 20%)	
Acute coronary syndromes	<100 mg/dl
AMI plus a ER disease	optional
AMI plus by-pass or PTCA	<70 mg/dl
High risk (greater than 20%)	
AMI	
"Equivalent Risk" diseases	
Stroke/TIA	
Arteritis obliterans in the lower limbs	<100 mg/dl
Abdominal aortic aneurysm	
Diabetes mellitus	
Moderate risk (10-20%)	<130 mg/dl
Low risk (<10%)	<160 mg/dl

Several pharmacovigilance trials have furthermore shown that there is a gap between the fixed goals and lipid values actually achieved in outpatient practice; this gap is greater, the more ambitious the lipid goal set. The percentage of patients who reach the fixed therapeutic goal is very modest (15-25%) for LDL values <100 mg/dl and their number is even lower if this limit is moved downwards, for example to 70-80 mg/dl. In the L-TAP trial, only 18% of patients treated with various statins at intermediate doses achieved the target set (LDL <100 mg/dl)<sup>13</sup>. In Ballantyne's recent trial, only 36% of patients treated with atorvastatin titrated to the maximum dose (80 mg/day) reached the 100 mg/dl goal; in this trial, however, the number of patients who reached the 70 mg/dl LDL value, defined as desirable in the new NCEP III 2004 guidelines, was around 13%.

The obstacles in the way of reaching the "desirable" lipid goals are of various nature but, besides prescriptive limitations associated with the need to control pharmaceutical expenditure, the fear of an increased risk of adverse events linked to use of the maximum doses seems

to be crucial. The need for a higher safety index is felt above all in general medicine, where the difficulty of implementing strict patient monitoring, particularly during the first weeks of treatment, constitutes a limit to increasing the dose through titration. On the other hand, the ezetimibe/simvastatin combination leads to greater decreases in LDL plasma concentrations with modest statin doses and, therefore, with a lower risk of adverse events, thus allowing more treated patients to reach the lipid goal.

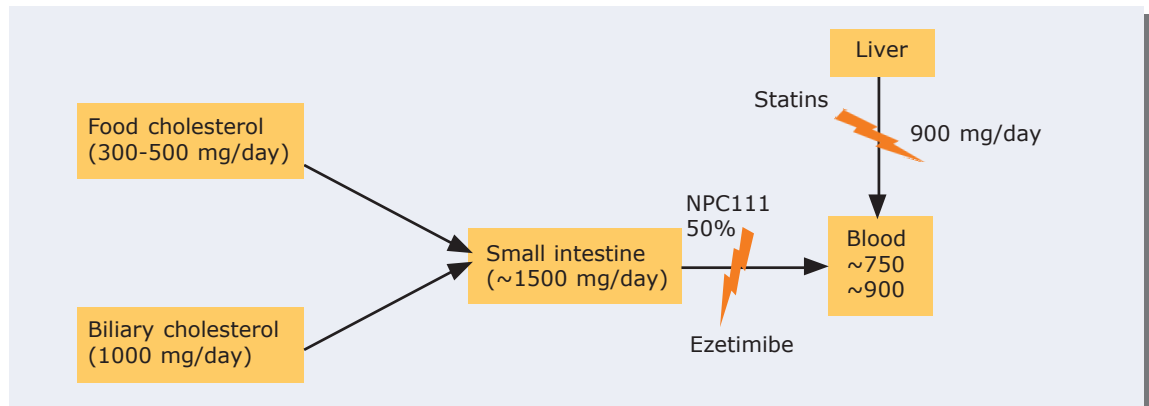
### Dual mechanism of action

In a healthy subject, about 60% of circulating cholesterol comes from hepatic synthesis (900 mg/day) and 40% from intestinal cholesterol absorption (600 mg/day). Homeostasis is ensured by effective control systems able to restrain or increase both the synthesis and absorption mechanisms<sup>14,15</sup>. Consumption of a standard western diet contributes the food equivalent of 300-500 mg/day of animal-origin cholesterol, to which biliary origin cholesterol needs to be added (1 g/day). The intestinal contribution to circulating cho-

lesterol is therefore significant, even if only 40-60% of intestinal cholesterol (1.5 g/day) is actually absorbed (figure 1).

If intestinal absorption is reduced, as occurs for example in gastroresected patients, the plasma concentrations are "compensated" by an increase in hepatic synthesis. Conversely, in patients with impaired hepatic biosynthesis, cholesterol absorption can increase to up to 90% of the intestinal pool<sup>16,17</sup>. Jejunum-ileal cholesterol absorption occurs thanks to a transmembrane carrier which binds to the cholesterol and carries it into the enterocytes. This carrier has recently been identified as protein NPC1L1 (Niemann-Pick C1 Like 1)<sup>18,19</sup>. Trials with tritiated ezetimibe have shown that both ezetimibe and above all its glucuronate metabolite are found firstly on enterocyte villi and later inside enterocytes themselves, in which both molecules accumulate<sup>20,21</sup>. Dose-finding trials have shown that administering ezetimibe for two weeks at a dose of 10 mg/day to moderately hypercholesterolaemic patients who consume about 350 mg of cholesterol/day in their diet, decreases cholesterol absorption by 54%<sup>22</sup>. The maximum inhibitory effect

**Figure 1.** Contribution of intestinal cholesterol (food and biliary) and hepatic cholesterol to the circulating total.



is obtained with this daily dosage, which is associated with a 15% decrease in total plasma cholesterol values (TC) and reduction in LDL-cholesterol (LDL-C) of around 21%. The drug has little or no effect on triglyceride absorption and does not interfere with liposoluble vitamin absorption<sup>23,24</sup>.

Ezetimibe has been approved both for monotherapy, only at a dose of 10 mg/day, and in combination with simvastatin at different doses (10, 20, 40 and 80 mg). The drug can therefore be used in monotherapy to treat mild hypercholesterolaemia and patients with intolerance to statins, but it is when it is combined with a statin that it shows its maximum effectiveness. Blocking intestinal absorption triggers an increase in hepatic synthesis which, if it is not suitably inhibited by a statin, tends to compensate (at least partially) for the decreased intestinal absorption caused by ezetimibe. Treatment with the ezetimibe/simvastatin combination therefore turns out to be complementary.

### Lipid lowering effectiveness of the dual mechanism of action

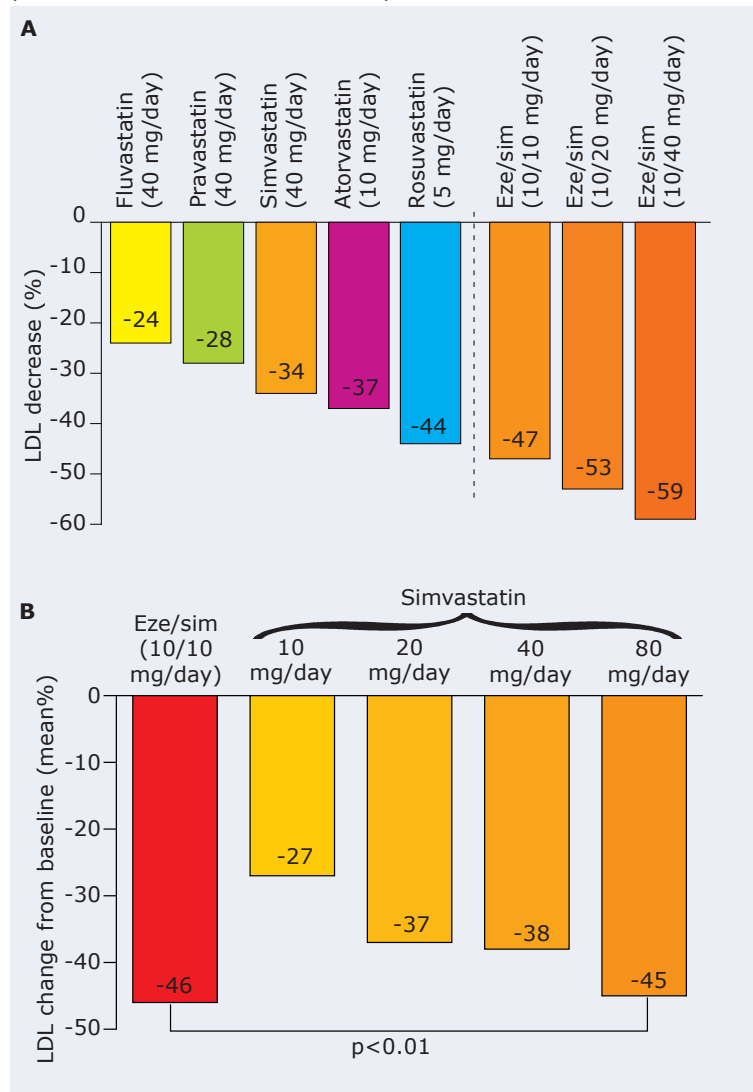
The effectiveness of the dual mechanism of action gives rise to objective pharmacological benefits: simvastatin, at a dose of 20 mg/day, leads to a LDL cholesterol decrease of 25-30% compared to baseline; if the same simvastatin dose is combined with 10 mg of ezetimibe/day, the LDL decrease reaches 40-45% compared to baseline. To obtain a similar LDL decrease with simvastatin, it has to be progressively titrated up to a dose of 40-60 mg/day. This example alone gives an idea of the favourable effects which

derive from the dual mechanism of action. Edwards' recent meta-analysis reported the dose-specific cholesterol lowering effects of the main statins used in controlled clinical trials<sup>25</sup>. Figure 2 compares the cholesterol lowering effects of the various statins examined in this meta-analysis with the cholesterol lowering effect of ezetimibe

combined with simvastatin at the three different doses observed in Feldman's trial (10, 20 and 40 mg/day)<sup>26</sup>.

On the whole, it can be said that adding ezetimibe to previous treatments with simvastatin at the usual dose (20 mg/day) leads to a further LDL decrease of about 20%. As can be seen in figure 2(B), the decreases obtained

**Figure 2.** (A) shows the effects of different statins at the most frequently used doses in controlled clinical trials and the ezetimibe-simvastatin combination. (Data from Edwards JE 2003 and Feldman T 2004). (B) shows the combined treatment (10 mg of ezetimibe/day + 10 mg of simvastatin/day) vs. 3-step simvastatin monotherapy titration: the results obtained with the monotherapy at maximum dose (80 mg/day) are comparable to the combined treatment at minimum dose. (Data from Davidson et al. 2002<sup>27</sup>).



ned with the combination at minimum doses are comparable to simvastatin monotherapy titrations at very high doses.

### *Other effects of ezetimibe*

The aforementioned trials confirm that combining ezetimibe with previous statin treatments improves other lipid parameters besides total cholesterol and LDL cholesterol. Significant results have been observed on triglycerides (about -11%), on HDL (about +2%), on the TC:HDL-C ratio (about -30%) and on C-reactive protein (about -10%). Since these parameters are involved in cardiovascular risk modulation, the clinical benefits are not presently quantifiable, but could be significant. Lastly Seedorf's recent experimental trial deserves to be mentioned, because a lower oxidized LDL "capture" by macrophages was observed in patients treated with ezetimibe<sup>28</sup>. Since the role of oxidized LDLs in "flooding" macrophages constitutes an essential step in the pathogenesis of atherosclerotic plaques, this characteristic could be extremely interesting and additional to the inhibitory effect on cholesterol absorption.

### *TC:HDL-C ratio*

The ratio between total cholesterol and HDL fraction is a very effective coronary heart disease predictor and, for this reason, it is indicated in all the guidelines as a parameter of significant clinical interest<sup>29</sup>. In the Canadian guidelines, this ratio is an explicit aim of the lipid lowering treatment (TC:HDL-C <3) and is additional to the LDL goal (<100 mg/dl) in patients with previously diagnosed coronary heart disease<sup>30</sup>. Clinical practice suggests however that it is very hard to reach this goal.

To give an example of the benefits of the ezetimibe/statin combination, it may be useful to look at the data obtained in a recent trial with ezetimibe from the point of view of the Canadian guidelines. In the Ballantyne et al. trial in 2003, the patients included had total cholesterol values of 261 mg/dl and HDL values of 51 mg/dl, with a TC:HDL-C ratio of 5.12<sup>31</sup>. To reach the goal set in the Canadian guidelines, these patients needed to decrease their LDL to values <100 mg/dl, with a TC:HDL-C ratio <3. To get this result, two distinct paths could be followed: 1) a very high decrease in total cholesterol with the same HDL-C level, for example reducing TC from 261 mg/dl (baseline) to 150 mg/dl (final); 2) a more "plausible" decrease in TC (from 261 to 180 mg/dl), but a considerable increase in HDL-C (from 51 to 60 mg/dl).

HDL changes of this size cannot be reached with statin monotherapy, even using maximum doses. In Ballantyne's aforementioned trial, statin monotherapy decreased total cholesterol levels by 32% (from 261 to 177 mg/dl): although significant, this percentage decrease would not have allowed the correct TC:HDL-C ratio to be reached (TC=177:HDL-C=53; ratio=3.3). Therefore, although the statin therapy was highly effective (atorvastatin), it would never have allowed the goal to be achieved. When the same population was treated with the combined treatment (ezetimibe/atorvastatin), total cholesterol decreased by 41% (from 261 to 154 mg/dl), and the HDL fraction increased by 7.3% (from 51 to 55 mg/dl) with a TC:HDL-C ratio of 2.8, i.e. in the range set down in the gui-

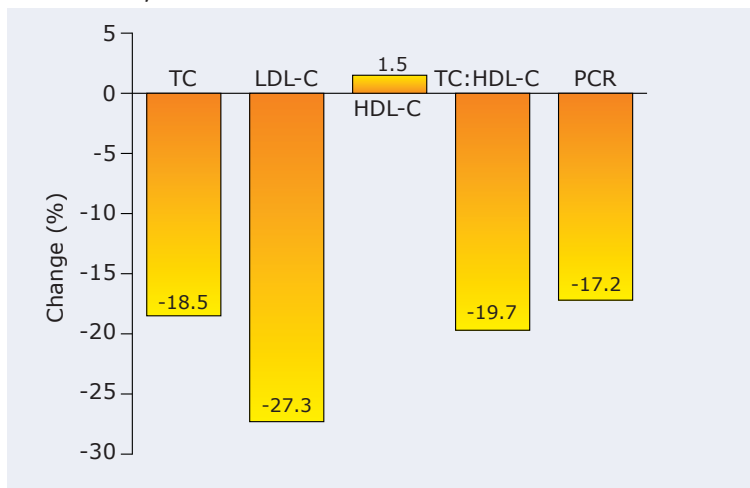
delines (TC:HDL-C <3). The results of this trial have been confirmed by other authors and give an idea of the effectiveness of ezetimibe treatment combined with a statin.

### *C-reactive protein*

CRP has been identified as a subclinical inflammation marker and seems to be directly involved in plaque instability phenomena<sup>32,33</sup>. Several clinical trials indicate values of CRP <3 mg/L as optimal, and suggest a progressive increase in risk as the plasma concentrations of this marker increase<sup>34</sup>. In 2003, the American Heart Association made the prognostic meaning of CRP official and suggested the usefulness of assessing this parameter with widespread screening in all patients with a cardiovascular risk >10%/10 years<sup>35</sup>.

How does the ezetimibe/simvastatin combination behave as regards C-reactive protein values? In a recent trial on patients with diabetes mellitus (DM) and metabolic syndrome (MS) with high CRP values, the combination of ezetimibe with various statins decreased C-reactive protein values by 17.2% in patients with DM and 6.5% in patients with MS<sup>36</sup>. It should be noted that this decrease occurred in patients already treated with statins. This data suggests two possibilities: 1) the existence of a direct relationship between ezetimibe and CRP values; 2) the existence of an indirect relationship, mediated by the greater cholesterol lowering activity of the combined treatment. Figure 3 summarizes the results of the combined treatment with ezetimibe in comparison with statin monotherapy only in the diabetes mellitus subpopulation.

Figure 3. Effects of ezetimibe/statin treatment compared to statin monotherapy in patients with diabetes mellitus. (Data from Simons L et al. 2004<sup>36</sup>).



The effects observed by Simons et al. have also been reported by other authors: in Goldberg's trial, ezetimibe (10 mg/day) monotherapy decreased this marker by 12.5% compared to baseline, while association with previous simvastatin treatment led to an average decrease of 8.7%<sup>37</sup>. The statin-independent efficacy of ezetimibe on CRP was also confirmed by Farnier in patients with familial combined hyperlipidaemia<sup>38</sup>. On the basis of these "chance" confirmations, Sager et al. specifically studied the effects of combining ezetimibe with previous simvastatin treatment in a large cohort of patients with primary hypercholesterolaemia<sup>39</sup>. In this trial, combining ezetimibe with simvastatin (10, 20, 40 or 80 mg/day) led to a decrease in CRP which was more than twice that achieved with statin monotherapy (33.3% *vs.* 14.3%;  $P < 0.01$ ). These effects were observed independently of sex, body mass index and baseline LDL values.

### Oxidized LDLs

The fatty streak and subsequent plaque formation process de-

pends directly on oxidized LDLs passing from systemic circulation to the sub-endothelium<sup>40,41</sup>. In a recent experimental trial, it was shown that activated macrophages express protein NPC1L1 - the same protein found in brush border enterocytes - and annexin-2 and caveolin-1, the protein mediators needed to bind ezetimibe to NPC1L1<sup>28</sup>. Ezetimibe is able to form heterocomplexes in macrophages with annexin-2 and caveolin-1, and the bond with these two proteins is able to block the oxidized LDL influx by about 50% in a dose-dependent way. If these results are confirmed in other experimental models, they could lead to new strategies to control the atherogenic process.

### Trials

In the last ten years, ezetimibe has been tested in experimental and clinical trials, first of all in monotherapy and subsequently in combination with all existing statins, and - in at least one case - with fibrates<sup>31,36,42-44</sup>. The results of these trials agree that ezetimibe monotherapy at the stan-

dard dose of 10 mg/day has a cholesterol lowering activity on LDLs of between 20 and 25% compared to baseline. This decrease is additional to that achieved with concurrent statin administration. The trials reported below are useful to see if, and to what degree, the ezetimibe/simvastatin combination may contribute towards filling the gap between the LDL goals fixed in the guidelines and the results actually achieved in outpatient practice. Table 2 summarizes the results of the most significant trials carried out with the ezetimibe/statin combination<sup>31,36,42-47</sup>.

The results of these trials show that adding ezetimibe (10 mg/day) to a pre-existing treatment with statins, without changing the statin dose, leads to an additional LDL decrease of nearly 25%<sup>26,37,49</sup>. On the whole, observational trials may be divided into two groups:

1. ezetimibe plus statins *vs.* statin monotherapies
2. ezetimibe plus simvastatin *vs.* statin monotherapies.

### Ezetimibe plus statin vs. statin monotherapies

Ezetimibe has been combined with all the statins available at present, and has always shown additional lipid lowering effects of the same size (20-25%) compared with statin monotherapies, regardless of the statin and its initial dose<sup>27,50,51</sup>.

The EASE trial is at the moment the most extensive in size and clinical sample profile (3,030 patients), and in terms of the variety and dose of statins with which ezetimibe has been combined<sup>48</sup>. The trial included both secondary prevention and high risk primary prevention patients. Adding ezetimibe led to a statistically significant de-

**Table 2.** Effects of combining ezetimibe (10 mg) with several statins (different doses) recorded in various trials.

Author (year)	Pat. (n°)	Trial	Results/comments
Davidson (2002) <sup>27</sup>	668	Eze (10 mg/day) plus Sim (10, 20, 40, 80 mg/day) vs. Sim monotherapy (10, 20, 40, 80 mg/day)	The combined treatment was found to be better than simvastatin monotherapy at all the doses used. The LDL decrease was 44% vs. 27%, 45% vs. 36%, 53% vs. 36% and 57% vs. 44%.
Ballantyne (2003) <sup>31</sup>	628	Eze (10 mg/day) plus Ato (10, 20, 40, 80 mg/day) vs. Ato monotherapy (10, 20, 40, 80 mg/day) x 12 weeks	The combined treatment was always found to be better than the monotherapy at each atorvastatin dose: 53% vs. 37%, 54% vs. 42%, 56% vs. 45% and 61% vs. 54%. Furthermore the combined treatment significantly decreased total cholesterol and triglycerides, with an 8% increase in HDL-C and 10% in hs-CRP.
Feldman (2004) <sup>26</sup>	710	Eze (10 mg/day) plus Sim (10, 20, 40, mg/day) vs. Sim (20 mg/day) x 23 weeks	The aim was to achieve the goal by titrating the dosage every 6 weeks if necessary. At the end of the fifth week 75%, 83% and 87% of the patients following the Eze+Sim treatment (10, 20, 40 mg/day) achieved the goal, compared with 46% of the monotherapy patients (20 mg/day); to reach the aim (LDL<100 mg/dl), 68% of the monotherapy patients required titration up to the maximum Sim dose (80 mg/day).
Simons (2004) <sup>36</sup>	769	Eze (10 mg/day) in addition to the previous treatment with various statins at different doses x 8 weeks	High risk patients (67.8%); 191 with DM (24.8%) and 195 with MS (25.4%); adding Eze led to a further LDL decrease in 27.3% of patients with DM and 23.2% of patients with MS; the LDL goal was achieved in 17.5% of DM patients and 27.2% of MS patients treated with the monotherapy, compared with 83.6% and 71.8% in the case of combined treatment.
Ballantyne (2005) <sup>45</sup>	1,902	Eze/Sim from 10/10 to 10/80 mg/day vs. Ato from 10 to 80 mg/day x 6 weeks	Primary (54%) and secondary prevention patients (46%); the combined treatment decreased LDLs by an average of 53.4% compared with the 45.3% of Ato, and increased HDLs by 7.9% against the 4.3% of Ato; at the intermediate dose (10/40 mg), 90% of the patients receiving the combined treatment achieved the LDL goal of <100 mg/dl compared with 23% treated with Ato; the LDL goal of <70 mg/dl was achieved at the same dose by 57% of patients with the combined treatment and by 23% with the monotherapy.
Brohet (2005) <sup>44</sup>	418	Eze (10 mg/day) or placebo in addition to Sim (10 or 20 mg/day) x 6 weeks	Patients with diagnosed CHD; adding Eze led to a further average LDL decrease of 27.1% and TG decrease of 11% compared to baseline; 17.4% of patients treated with Sim and 80.4% of patients treated with Eze/Sim achieved the LDL goal (<100 mg/dl).
Pearson (2005) <sup>48</sup>	3,030	Eze in addition to previous treatments with various statins at different doses x 6 weeks	Secondary (77%) and primary protection (23%) patients; adding Eze further decreased LDLs by 25.8% compared to the statin monotherapy, independently of the drug, age, sex and ethnic group; the NCEP III goal went from 20.6% (monotherapy) to 71% (combined treatment).
Gaudiani (2005) <sup>47</sup>	214	Eze/Sim (10/20 mg/day) vs. Sim 40 mg/day x 24 weeks	Patients with DM-2 treated with glitazones; adding Eze to the standard Sim dose (20 mg/day) led to a 20.8% greater decrease in LDLs than that achieved with twice the dose of Sim (40 mg/day); the LDL goal was achieved by 75.5% of patients treated with Eze/Sim(10/20) and 39.4% of patients receiving Sim monotherapy (40 mg/day).

Key: Eze=ezetimibe; Sim=simvastatin; Ato=atorvastatin; Pra=pravastatin; DM-2=type 2 diabetes mellitus; MS=metabolic syndrome; TG=triglycerides.

crease in blood cholesterol-LDL minus placebo effect of 23%, regardless of the statin and dose administered. All treated patients benefited from the addition of ezetimibe regardless of their initial LDL values, sex and the type of statin administered; important results were also obtained on triglycerides (with a net improvement of 11.2%) and on apo B (-16.3%); the results on HDL (+2.1%) were modest (figure 4).

As can be seen in figure 4, in the case of patients with CHD or diseases with equivalent risk (ER), adding ezetimibe to any statin brings about 50% of them in line with the NCEP goal.

#### **Ezetimibe plus simvastatin vs. other statins**

The effects of the ezetimibe/simvastatin combination have been compared with those obtained with atorvastatin, and trials against rosuvastatin are still under way. The most important comparative trial available at present is the VYVA (The VYtorin Versus Atorvastatin Study), carried out by the Balantyne group on a population

of 1,902 primary (1,023) and secondary (879) prevention patients<sup>45</sup>. One of the mandatory criteria for inclusion was failure to reach the LDL-C goals fixed according to the NCEP III criteria for the various risk factor groups: <100 mg/dl for high risk patients; <130 mg/dl for medium risk patients; <160 mg/dl for low risk patients.

The patients were assigned randomly to eight treatment groups: four received ezetimibe (10 mg/day) combined with simvastatin (10, 20, 40, 80 mg/day), while the four comparison groups received atorvastatin monotherapy (10, 20, 40 and 80 mg/day). The primary aims were to assess the effectiveness of the treatment on the lipid parameters and achievement of the NCEP III and NCEP III 2004 goals (LDL <70 mg/dl); the secondary aims were to assess any adverse events (increase in ALT/AST and cases of myopathy) for each treatment schedule. The treatment duration was fixed at six weeks. At the end of the trial, a significantly better result was recorded in each combined treatment group

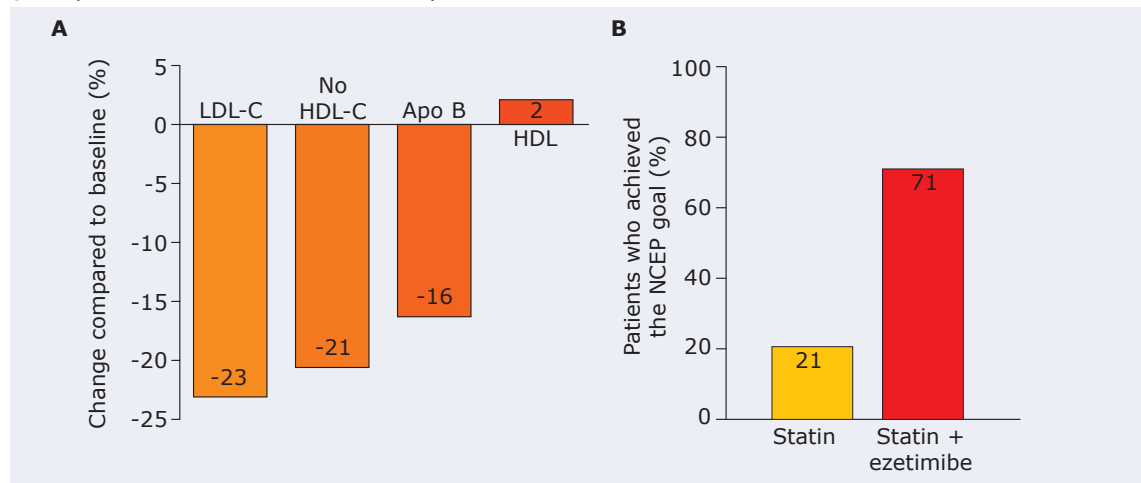
than in the corresponding control group, for both the primary aims and the adverse events. The trial results are summarized in figure 5.

Only 20% of the patients treated with atorvastatin at maximum dose reached the LDL <100 mg/dl goal in this trial; this result was achieved by twice as many patients treated with the combined drugs at maximum dose (45%). An increase in transaminase >3 times the maximum limit was recorded in 1.2% of the patients treated with atorvastatin and 0.1% of those treated with the combination.

#### **Who should be treated with ezetimibe/simvastatin?**

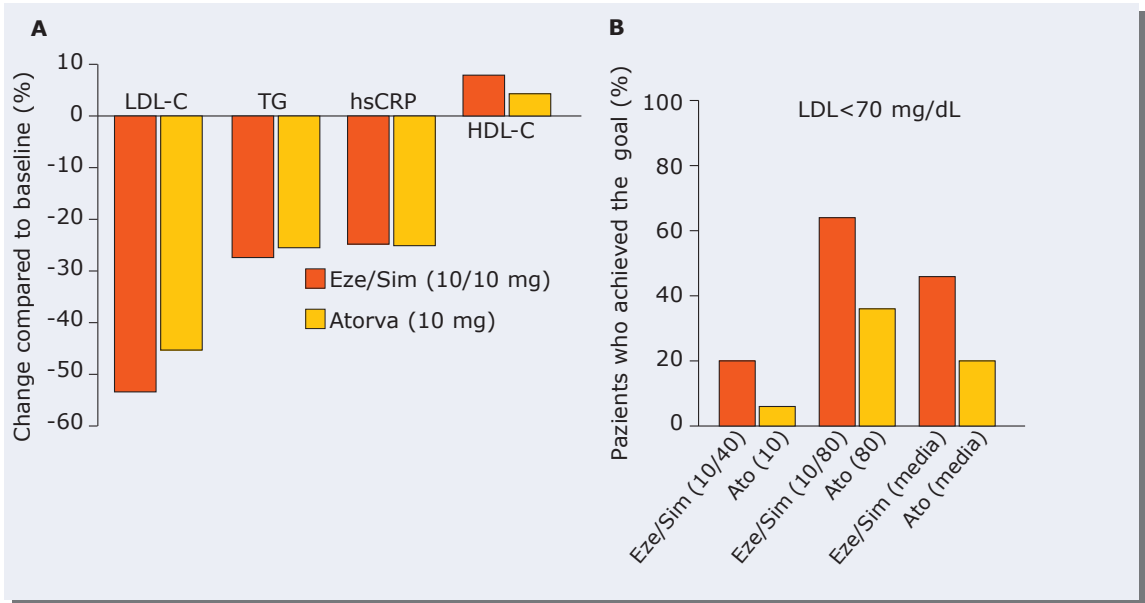
Identification of candidate patients for the combined treatment is an essential condition for appropriate use of the drug. In principle, the candidate patients for elective therapy with ezetimibe/simvastatin are those for which statin monotherapy does not effectively control hypercholesterolemia. This may

**Figure 4.** Results - net of placebo effect - on the main lipid parameters after adding ezetimibe to previous statin treatments (A); (B) shows the effects of the treatment on the NCEP III (LDL <100 mg/dl) goal. (Data from Pearson *et al.* 2005<sup>48</sup>).





**Figure 5.** (A) shows the effects of ezetimibe (10 mg) plus simvastatin (10 mg/day) on the main lipid parameters, compared with atorvastatin monotherapy (10 mg/day). (B) shows the effects on the number of patients within the goal. (Data from Ballantyne C. *et al* 2005<sup>45</sup>).



occurs because the patients poorly tolerate high doses or because they respond poorly to statin treatment. The need for a safe effective combined treatment therefore remains. Ezetimibe is characterized by a high safety profile, and its addition to simvastatin at usual doses (20 mg/day) - a drug which is so safe it has been classified in some countries as an over-the-counter product - leads to an LDL "improvement" equal to that which can be obtained with simvastatin at a dose of 60-80 mg/day, i.e. comparable to that which could be obtained with the most recent statins at high doses. This pharmacological "improvement" is however obtained with a lower risk of myopathy, which is the main statin titration limiting factor.

Patients who respond poorly to statins should also be considered ideal candidates: having a double mechanism of action allows this population to achieve therapeutic goals without having to increase excessively the do-

ses, thus recovering significant numbers of non-responders. Furthermore combined treatment is necessary for all patients who do not reach LDL goals (table 3).

### Expected benefits on clinical-end points

The final aim of any lipid lowering treatment is a decrease in coronary events (fatal and non-fatal), revascularization rates, incidence and relapse time. These effects can only be measured in properly designed clinical trials as regards number of patients and treatment duration. Various meta-analyses have shown that the clinical effects of lipid lowering treatment become tangible from the third year onwards and that the decrease in LDL is proportional to the decrease in corresponding risk of coronary events for a wide range of values (from about 160 to about 80 mg/dl)<sup>2,52-54</sup>. In this range of LDL values, it may be assumed that:

**a 1 mg/dl LDL decrease =  
a 1% decrease in the  
relative risk**

This relationship is independent of the lipid lowering drug used. At present data relating to the benefits of the combination treatment with ezetimibe on the above mentioned clinical endpoints is not yet available, but clinical trials have been specially designed<sup>55,56</sup>. Nevertheless, on the basis of what has been established up to now, we can assume that the aforementioned relationship holds for ezetimibe too, as it does for statins, other lipid lowering drugs and jejunum-ileal surgical bypass procedures (POSCH trial)<sup>57,58</sup>.

In Knopp *et al.*'s trial, administration of 10 mg of ezetimibe/day decreased LDLs by about 30 mg/dl (from baseline values of about 165 mg/dl to final values of 135 mg/dl)<sup>23</sup>. In combination trials, similar (and additional) decreases in plasma LDLs are reported, generally from 25 to 30 mg/dl<sup>37,49</sup>. On the

**Table 3.** Candidates for elective therapy with ezetimibe/simvastatin.

Clinical condition	Comment
• CHD plus diffuse atherosclerosis or diabetes or TIA	• Patients classified at very high risk in the NCEP III 2004 guidelines
• Diabetes plus bypass or PTCA	• High risk of new events and restenosis
• Acute coronary syndromes (ACS)	• Patients at high thrombotic risk
• Intolerant patients	• Early hypertransaminasaemia even at low doses
• Poorly responding patients or with high baseline LDL levels (> 180 mg/dl)	• High doses of statin are not able to reach the goal
• Homozygous familial sitosterolaemia	• In addition to plasmapheresis and dietary restrictions

Key: PTCA=percutaneous transluminal coronary angioplasty; ACS=acute coronary syndromes; MS=metabolic syndrome; CHD=Coronary Heart Disease.

basis of the above mentioned relationship between LDL concentrations and respective risk, these LDL decreases translate into an (additional) decrease in coronary events of 25-30%. A decrease in coronary risk of this size is comparable to that obtained with statins at intermediate doses, for example in the CARE, LIPID and HPS trials<sup>59-61</sup>.

In the HPS trial, an LDL decrease of about 1 mmol/l (39 mg/dl) led to a 27% decrease in major coronary event risk and 38% decrease in non fatal AMIs.

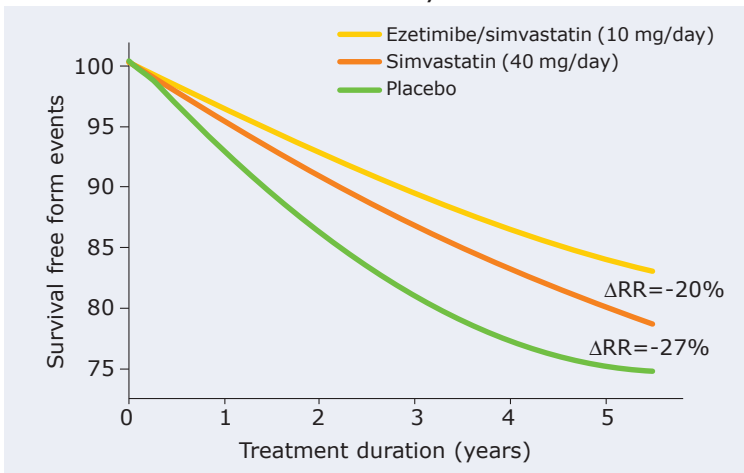
It can therefore be claimed that a 30 mg/dl LDL decrease obtained by adding ezetimibe decreases the risk of non fatal AMIs by 30% (ratio 1:1) and major coronary events by about 20% (figure 6).

In conclusion, if the patients in the HPS trial had been treated with simvastatin (40 mg/day) combined with ezetimibe instead of simvastatin alone at the same dose, the decrease in major coronary event risk would presumably have been of 45-50% instead of 27%.

### **Economic aspects of the combined treatment**

The combined treatment allows more than twice the number of patients to achieve the therapeutic goal and therefore fully benefit from a correct lipid lowering therapy. The alternative to the combined treatment consists of titrating statin until the goal is achieved. Since the combination costs considerably more than the monotherapy, but this difference becomes progressively smaller with statin titration and the appearance of any adverse events, the clinical benefits of the two options were recently compared in a pharmacoeconomic model<sup>62</sup>. In this analysis, three distinct cohorts of patients from three different health backgrounds (Germany, Spain and Norway) were analysed from a cost/effectiveness point of view after using both therapeutic strategies. The patients included in this analysis had CHD or diabetes and were not within the LDL goal values. The additional cost of the combined treatment compared with non-titrated statin monotherapy was € 18,000 for every life-year gained (LYG) and € 26,000/LYG

**Figure 6.** Effects on major coronary events (MCE) stemming from treatment with ezetimibe plus simvastatin compared with simvastatin monotherapy. The effects were forecast for a high risk population on the basis of the results of the HPS study.



with titrated statin treatment. In high risk populations, the combined treatment turned out to have a good cost/effectiveness ratio when compared to the alternative strategy (statin titration).

## Conclusions

In the light of what we have reported, statins remain the front line drug for the majority of patients with coronary heart disease. However the recommendations in the most recent guidelines cannot be disregarded, in particular as far as the LDL goal is concerned. On the basis of these recommendations, all high coronary risk patients should decrease their plasma LDL-C concentrations to values of <100 mg/dl. The optional limit suggested by the most recent 2004 NCEP-III document (LDL <70 mg/dl) is objectively very ambitious in clinical prac-

tice and difficult to achieve in patients which cannot easily be strictly monitored. Although it is little used in clinical practice in Italy and other European countries, the TC:HDL-C ratio <3 goal suggested by the Canadian guidelines as high priority and as having the same validity as the LDL <100 mg/dl limit, should also be taken into consideration, since it is a more effective predictor of clinical events than LDLs.

In this context, adding ezetimibe to previous statin treatments may be the only really effective and safe choice for reaching the goals set. The patients who benefit most from combined treatment are those at high atherothrombotic risk (including diabetics and patients with metabolic syndrome), all those who respond poorly to statin treatment, and those with baseline serum cholesterol levels which are too high to be effectively

decreased with statin monotherapy, even at high doses. Although the results of trials able to measure the effects of ezetimibe treatment on clinical endpoints will only be available in the next 2-3 years, as things stand, it is reasonable to expect that the 20-30% improvement in LDL decrease achieved by co-administration of ezetimibe should be associated with an equal decrease in clinical events.

The combination treatment is also the safest way to bring high percentages of patients who would not have otherwise completely benefited from the long-term advantages of correct lipid lowering therapy within therapeutic target levels. **TiM**

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