The strong positive correlation between plasma low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) mortality has been documented beyond any doubt.\(^1\) A large body of trials aiming at reducing elevated LDL-C levels also shows that therapeutic intervention results in a proportional reduction of CV events independent of the type of intervention (i.e. diet versus drugs or surgical interventions).\(^2-3\) These data are reflected in guidelines that aim at reducing elevated LDL-C levels also shows that therapeutic intervention results in a proportional reduction of CV events independent of the type of intervention (i.e. diet versus drugs or surgical interventions).

The results from these trials are in line with the guidelines of several international health organisations that indicate lower LDL-C goals in patients with coronary heart disease (CHD) and/or diabetes. For example, the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines suggest that patients with diabetes and CV disease (CVD) be treated to below 70mg/dl. New guidelines from the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) also include an LDL-C goal of <70mg/dl for secondary prevention of CV events in patients with diabetes and symptomatic CVD, and a goal of <97mg/dl for primary prevention in patients with diabetes without symptomatic CVD.\(^4-9\)

For patients with established coronary artery disease (CAD), a reduction in LDL-C of at least 50% is generally required to prevent progression or elicit regression of atherosclerosis. A linear regression analysis from different intravascular ultrasound (IVUS) studies showed that there is a very high correlation between mean LDL-C levels achieved in the various studies and the mean progression rate of atherosclerosis.\(^10\)

Clinical practice, however, is still far from reaching these goals. Several studies have documented a significant gap between the treatment guidelines and the actual treatment status in dyslipidaemic patients in primary and secondary prevention. This was confirmed in the REALITY study,\(^11\) which demonstrated that more than 60% of patients did not achieve the LDL-C target goal of 100mg/dl (see Figure 1). Interestingly, only 16% of statin regimens were adjusted to increase potency with the final aim of achieving the recommended plasma LDL-C levels. In the cardiology department setting, the EUROASPIRE II study,\(^12\) conducted in 15 countries, showed that 61% of patients were taking lipid-lowering drugs at interview and only 51% of the patients on lipid-lowering therapy reached the total cholesterol goal of <190mg/dl. In addition, large variations between different countries were observed (see Figure 2). Understanding the reasons behind this is of paramount importance and efforts should be aimed at modifying this pattern in clinical practice.

Failure of statin monotherapy to achieve LDL-C target goals can be attributed to the fact that the initial dose of statins always produces the biggest proportionate reduction in LDL-C levels.

1. The fear of side effects. This plays a role in the decision not to uptitrate the statin dose. The incidence of side effects is dose-related for statins, with the most frequent side effects being increased liver
Cholesterol Management

enzyme plasma levels and muscle pain – usually with an increase of creatine phosphokinase (CPK).

Together, these findings have contributed to our understanding of the limitations of lipid-lowering therapy using a single drug.

In recent years, cholesterol absorption inhibitors – a new class of hypolipidaemic drug – have been made available to physicians. Ezetimibe is the first molecule in this class. The mechanism by which ezetimibe inhibits cholesterol absorption is linked to its interference with the NPC1L1 protein, which is involved in cholesterol absorption in the gut. As intestinal cholesterol derives mainly from the liver and from the intestine, interfering specifically with cholesterol absorption results in an average reduction of 18–20% of LDL-C.

The mechanism of action of ezetimibe induces a feedback response and increases cholesterol production in the liver. This effect somehow limits the efficacy of ezetimibe and makes co-administration with statins (drugs that interfere with cholesterol production) the ideal approach to a further and more effective reduction of plasma LDL-C levels, as the two main pathways that regulate cholesterol in the body – production and absorption – are targeted. The co-administration of ezetimibe with a statin, especially at low statin doses, brings about a further LDL-C decrease of 20–24%. This result is superior to that achieved with a 3–4-fold increase of the statin dose, and results in a better achievement of therapeutic goals. This is recapitulated in recently published studies comparing the efficacy of ezetimibe/simvastatin single tablet with atorvastatin in terms of LDL-C goal attainments. Data on LDL-C goal attainment for 100 and 70mg/dl are presented in Figures 3 and 4. This evidence clearly shows a statistically significant greater achievement of LDL-C goals with ezetimibe/simvastatin single tablet. Of note, the pattern of side effects detected during these studies is either similar to or in favour of those detected with ezetimibe/simvastatin single tablet.

Conclusions
Standard statin doses are often insufficient to achieve LDL-C goals and many patients need more intensive LDL-C-lowering therapy. In order to maximise clinical benefits, clinicians should initiate a suitable lipid-lowering drug at an appropriate dose that will have a high probability of reaching target. Physicians can also co-administer lipid-lowering drugs with different mechanisms of action (e.g. ezetimibe co-administered with a statin) to achieve better LDL-C goal attainment.

The paradigm of drug association is not new. Hypotensive drugs are widely used in association to better control elevated blood pressure. This approach has been less popular in the field of dyslipidaemia. The availability of new safe and effective therapeutic options, however, will certainly increase the co-administration approach and help to reduce the cardiovascular burden for many at-risk patients in our society.

![Figure 1: LDL-C Goal Attainments in Different Settings in General Practice in Europe (The REALITY Study)](image)

- **France**: 55% patients receiving therapy
- **Germany**: 24% patients receiving therapy
- **Italy**: 14% patients receiving therapy
- **Spain**: 26% patients receiving therapy

**LDL-C goal of <100mg/dl (<2.6 mmol/l) per NCEP Adult Treatment Panel III (ATP III) guidelines.**

**UEOASPIRE II: Control* of Hyperlipidaemia at Interview**

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<thead>
<tr>
<th>Country</th>
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<th>Treated/uncontrolled</th>
<th>Treated/controlled</th>
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*Among those with total cholesterol ≥ 4.0mmol/l and/or under lipid-lowering drugs.
Figure 3: LDL-C Goal Attainments with Ezetimibe/Simvastatin Single Tablet versus Atorvastatin

Ezetimibe/Simvastatin provides superior goal attainment (<100 and <70mg/dl) across the dose range than Atorvastatin in high-risk patients **

Results from the VYVA study. Data are expressed as the percentage of patients achieving the LDL-C goals of 100mg/dl (left panel) and 70mg/dl (right panel). Ballantyne CM et al., Am Heart J. 2005;149:464–73.

Figure 4: LDL-C Goal Attainments with Ezetimibe/Simvastatin Single Tablet versus Rosuvastatin

Results from a multicentre study. Data are expressed as the percentage of patients achieving the LDL-C goals of 100mg/dl (left panel) and 70mg/dl (right panel).


15. Catapano AL, unpublished.


