


# ‘Use of lipid-lowering therapy: the guidelines, the drugs or the patient?’

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## KEYWORDS

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The current step up approach in the therapy of dyslipidemias aims to reduce the amount of LDL cholesterol below a threshold that varies according to the patient’s risk category, with a pharmacological approach that sees statins as a fundamental cornerstone. Although absolutely functional in reducing cardiovascular events, this therapeutic algorithm does not yet take into consideration the innumerable phenotypic variables that we can find in dyslipidemic subjects. The ever finer understanding of the pathophysiological mechanisms underlying dyslipidemias in combination with the novelties obtained through DNA genotyping will allow, in the near future, the development of a ‘tailor-made’ therapy for each category of patients. This article will summarize the most recent evidence regarding the therapy of dyslipidemias, with particular attention to the concept of cumulative exposure and some hypotheses on possible initial therapeutic proposals in patients with diabetes, vasculopathy, with hypertriglyceridaemia and with high levels of Lp (a).

## Introduction

The achievement of a certain serum concentration of LDL cholesterol has always been the main therapeutic target of the lipid-lowering drugs available, but not only the achievement of an LDL cholesterol value below the target determined by the risk category by means of a sequential approach would seem to be the only goal that clinicians tend to pursue but also considering the countless variables that could modify the therapeutic strategy to be adopted. The purpose of this article is to provide the most recent evidence regarding the therapy of dyslipidemias, in such a way as to favour a 360° personalized approach for each patient based on individual characteristics.

## The main lipoproteins and the risk of cardiovascular events: beyond LDL cholesterol

LDL cholesterol (LDL-C), the main circulating Apo B-containing lipoprotein, currently represents the

pivotal target of the majority of lipid-lowering therapies available; this is because on the one hand there is a vast body of literature that agrees in associating the serum concentration of this molecule with the risk of cardiovascular disease,<sup>1</sup> on the other hand, there is evidence of how a reduction in LDL-C is associated with a consensual lower incidence of cardiovascular events. In particular, each 39 mg/dL decrease in LDL-C is associated with a 21% decrease in cardiovascular events.

Recently also triglycerides, initially considered as ‘secondary actors’, have returned to the centre of attention: compared with subjects with a triglyceride concentration lower than 90 mg/dL, it has been shown that as this value increases, there is an increase in incidence of myocardial infarction, unstable angina, and need for revascularization, up to a risk greater than 52% in subjects with a value greater than 354 mg/dL (HR: 1.52, 95% CI: 1.36-1.71,  $P < 0.0001$ ).<sup>2</sup> Similarly, in the IT-TIMI trial, it emerged that in patients treated with statins following a cardiovascular event, a reduction in the concentration of triglycerides below 150 mg/dL is associated with a reduction in the risk of coronary ischaemic disease, independent of LDL-C levels; in particular, for

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each reduction of 10 mg/dL in the concentration of triglycerides, a reduction of 1.6% was observed in the composite endpoint ( $P < 0.001$ ).<sup>3</sup>

Last but not least, we find lipoprotein (a) [Lp (a)]: it is an LDL-like lipoprotein synthesized by the liver containing Apo B 100 linked to apolipoprotein (a). The production of this molecule is largely under genetic control and an increase in its plasma concentration is associated with a progressive increase in cardiovascular risk due to its pro-atherogenic, pro-inflammatory, and pro-thrombotic properties, regardless of the concentration of LDL-C.<sup>4</sup>

### The concept of cumulative exposure: when to start lipid-lowering therapy?

Studies conducted in patients with familial hypercholesterolaemia have introduced the concept of cumulative exposure, which clinicians must consider when approaching the dyslipidemic patient. It is not enough, in fact, to evaluate only the concentration of total cholesterol and LDL-C, but it will be necessary to take into consideration how long the patient has been exposed to certain cholesterol levels, for example: a subject suffering from homozygous familial hypercholesterolaemia will begin to develop signs of ischaemic coronary artery disease at 12.5 years, whereas a patient with heterozygous familial hypercholesterolaemia will achieve the cholesterol burden necessary to develop ischaemic coronary artery disease at 35 years without treatment; this natural history can be modified by the timely decision to undertake lipid-lowering therapy.<sup>5</sup> Pencina *et al.* hypothesized how an aggressive therapeutic approach undertaken early in adulthood, especially in all subjects with non-HDL cholesterol values  $>160$  mg/dL, can significantly reduce the medium to long-term risk of cardiovascular disease: starting lipid-lowering therapy in a patient aged 40 to 49 years with a non-HDL cholesterol value  $>160$  mg/dL would reduce the 30-year risk of cardiovascular disease from 17.1% down to 6.5%.<sup>6</sup>

### The approach of current ESC guidelines in patients with high LDL cholesterol levels: beyond statins

According to the latest ESC 2019 guidelines,<sup>1</sup> lipid-lowering therapy should be optimized on the basis of cardiovascular risk calculated by SCORE, LDL-C levels, and the presence or absence of diabetes mellitus with or without organ damage, hypertriglyceridaemia (defined as a triglyceride concentration  $>310$  mg/dL), markedly elevated LDL-C ( $>190$  mg/dL), presence of systemic arterial hypertension with values  $\geq 180/110$  mmHg, presence of familial hypercholesterolaemia, moderate or severe chronic kidney disease and clinical evidence or by imaging of atherosclerotic cardiovascular disease. On the basis of the combinations of these parameters, the risk categories will be defined with the respective LDL-C target that is: low risk (LDL-C  $< 116$  mg/dL); moderate risk (LDL-C  $< 100$  mg/dL); high risk (LDL-C  $< 70$  mg/dL);

very high risk (LDL-C  $55 < \text{mg/dL}$ , up to  $<40$  mg/dL). The subsequent approach involves, in the case of an indication for lipid-lowering drug therapy, the use of a high-potency statin at the maximum tolerable dose; subsequently, the possible addition of ezetimibe will follow if the LDL-C levels are not yet optimal for the patient's risk category and, as a last resort, the use of PCSK9 inhibitors (PCSK9i). But how can we customize this approach following a rationale that takes into account the phenotype of each patient and the pharmacodynamic mechanism of the medicines we have available? We will list, below, the drugs that modern clinicians have available beyond the 'classic' statins and the categories of patients in which these molecules can satisfy, in some cases, this need:

#### Ezetimibe

The mechanism of action of ezetimibe lies in the inhibition of a protein responsible for regulating the absorption of cholesterol in the intestine, the Niemann-Pick C1-like 1 (NPC1L1) protein. As a consequence, the amount of cholesterol that reaches the liver will be reduced; this will result in a greater expression of LDL receptors on hepatocytes and a consequent reduction in LDL-C. On average, the addition of 10 mg of ezetimibe to a lipid-lowering therapy with a statin is effective in reducing the share of LDL-C by 23-24% and represents the second therapeutic step in the ESC algorithm.

#### Ezetimibe in patients with Type II diabetes mellitus

In subjects suffering from Type II diabetes mellitus, for example, an upregulation of intestinal NPC1L1 mRNA has been demonstrated with a possible consequent increase in the absorption of biliary cholesterol and newly synthesized intestinal cholesterol.<sup>7</sup> These considerations led to the analysis of the efficacy of ezetimibe combined with simvastatin vs. placebo combined with simvastatin in a subgroup of diabetic patients from IMPROVE-IT<sup>8</sup>: a frequency in the composite primary endpoint for cardiovascular death, major coronary events was observed, and 7-year non-fatal stroke by 40% vs. 45.5% in patients treated with statin/ezetimibe vs. statin/placebo. Diabetic patients treated with statin/ezetimibe had significantly lower HRs in endpoints for myocardial infarction (HR: 0.76; 95% CI: 0.66-0.88;  $P=0.028$ ), ischaemic stroke (HR: 0.61; 95% CI: 0.46-0.82;  $P=0.031$ ), and the composite for cardiovascular death, myocardial infarction, or stroke (HR: 0.80; 95% CI: 0.71-0.90;  $P=0.016$ ) compared with non-diabetic patients. It is interesting to note that the reduction of the primary endpoints was evident and significant especially in diabetic patients aged less than 75 years (HR: 0.87; 95% CI: 0.78-0.96;  $P=0.008$ ).

In diabetic patients, it is therefore rational to hypothesize how an initial therapeutic approach already consisting of a statin in combination with ezetimibe could be advantageous.

## PCSK9 inhibitors

The proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme performs its function by binding to the LDL cholesterol receptor (LDLR), mediating endocytosis and subsequent degradation within the cells; this results in a reduction in the reabsorption of LDL-C by the hepatocytes and a consequent increase in the amount of circulating LDL cholesterol. The PCSK9 inhibitors (PCSK9i) currently available on the market are monoclonal antibodies that block the activity of this enzyme, reducing the amount of LDL-C. Notably, both alirocumab and evolocumab were shown to be effective in reducing the composite endpoints for cardiovascular death, myocardial infarction, and stroke compared to placebo in the ODYSSEY Outcomes and FOURIER1 trials. Currently, these molecules are recommended in secondary prevention patients as a third line of therapy in addition to statin and ezetimibe in all patients who do not reach the optimal LDL-C target or in patients intolerant to statins in combination with ezetimibe. They are recommended in primary prevention for all very high risk patients with familial hypercholesterolaemia (FH) who do not reach the optimal LDL-C target and could be considered as primary prevention in very high risk patients without FH who do not reach the optimal LDL-C target despite therapy with the maximum tolerated dose of statin and ezetimibe.

## PCSK9i in patients with peripheral arterial disease

A further category that could benefit from the early addition of a PCSK9i is represented by patients with peripheral arterial disease (PAD): in these subjects the serum concentrations of PCSK9i were found to be significantly elevated compared with controls and a high serum concentration of PCSK9i was strongly associated with the risk of PAD<sup>9</sup> regardless of age, LDL-C, Lp (a), HDL-C, and statin treatment (HR: 1.46; 95% CI: 1.05-2.06;  $P=0.027$ ), although the risk is higher when associated with an increased concentration of Lp (a) (HR: 3.35; 95% CI: 1.49-7.71;  $P=0.0038$ ).

Furthermore, it must be considered that statins and ezetimibe, an integral part of the therapy of many patients with PAD, cause an increase in serum PCSK9 concentration mediated by the induction of the SREBP-2<sup>10</sup> pathway which could in part counteract the effects on the reduction of LDL-C. In the FOURIER study, it was found that the addition of Evolocumab compared with placebo significantly reduced the primary endpoint and the composite of cardiovascular death, myocardial infarction, or stroke in subjects with and without PAD<sup>11</sup>; however, it is interesting to note that the absolute risk reduction was greater in patients with PAD. It is possible to hypothesize how, in the case of patients with high levels of PCSK9 and largely taking statins and ezetimibe, the early addition of a PCSK9i to therapy may be advantageous, as well as logical and appropriate from a pharmacodynamic point of view.

## PCSK9i in patients with high Lp (a) values

In the FOURIER study, it was found that the risk of major coronary events was higher in patients with Lp (a) concentrations above the 90th percentile (96 mg/dL). The use of evolocumab, reducing the Lp (a) concentration by an average of 27%, reduced the risk of death from cardiovascular events, myocardial infarction or the need for urgent coronary revascularization by 16% compared with placebo (HR: 0.84; 95% CI: 0.76-0.93); this risk reduction would appear to be greater in patients with higher baseline Lp (a) levels.<sup>4</sup> The mechanism by which PCSK9i reduce Lp (a) levels is not yet known, although some evidence suggests a role both in the inhibition of production and in increased clearance through LDLR upregulation.

The levels of Lp (a) could therefore be used as a further element of additional risk in dyslipidemic patients, motivating an early introduction of PCSK9i into therapy.

## Icosapent ethyl

Icosapent ethyl is a stable ethyl ester of eicosapentaenoic acid, an omega-3 fatty acid. In the REDUCE-IT<sup>12</sup> study, the efficacy of this molecule in reducing the risk of cardiovascular events in a population of patients with hypertriglyceridaemia (defined as a fasting serum triglyceride concentration between 135 and 499 mg/dL) and known cardiovascular disease or diabetes mellitus and at least one additional cardiovascular risk factor, was investigated; administration of 4 g/day of icosapent ethyl reduced the relative risk for the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or unstable angina by 25% compared with placebo. In particular, the primary endpoint occurred in 17.2% of subjects receiving icosapent ethyl and in 22.0% of patients in the placebo group (HR: 0.75; 95% CI: 0.68-0.83;  $P<0.001$ ). All patients enrolled in the study had been on statin therapy for at least 4 weeks, with an LDL-C concentration ranging between 41 mg/dL and 100 mg/dL. It is interesting to note that the benefits on cardiovascular risk obtained were found to be independent of both the triglyceride levels obtained 1 year after the beginning of treatment and the starting triglyceride levels; this evidence suggests that the action of icosapent ethyl derives from the reduction of the concentration of triglycerides and acts according to still unknown mechanisms, thus filling a fundamental therapeutic need, namely the reduction of cardiovascular risk in subjects with hypertriglyceridaemia: in this category of patients, therefore, it may be reasonable to start therapy with icosapent ethyl early.

## A look to the (near) future in the therapy of dyslipidemias

In addition to the aforementioned drug classes, countless clinical trials are underway on different molecules that will allow a 'tailored' therapeutic approach for each category of patients:

Pelacarsen, an antisense oligonucleotide, will be the first drug aimed at reducing Lp (a) levels; its effectiveness

in reducing cardiovascular events in patients in secondary prevention, in addition to the simple serum concentration of Lp (a), is currently being studied in the HORIZON trial; these results will allow us to evaluate the early introduction of this therapy in patients with high levels of Lp (a).

Inclisiran, a siRNA designed to inhibit PCSK9 messenger RNA, has been shown to be effective in reducing LDL-C concentration. This drug, after administering the second and third doses, respectively, at 3 and 6 months, provides for maintenance only one injection to be practiced every 6 months; this approach will allow, in particular, to stem the problems related to poor therapeutic compliance and the increased risk of death and cardiovascular events linked to the variability of LDL-C in check-ups, ensuring a long-lasting lipid-lowering effect. In fact, it is worth remembering that in patients in secondary prevention, the variability in LDL-C levels must also be observed in follow-up visits: Bangalore *et al.* showed that each variation of one standard deviation is associated with an increased risk of death of 17% (HR: 1.17; 95% CI: 1.08-1.25;  $P < 0.0001$ ), cardiovascular events of 8% (HR: 1.08; 95% CI: 1.04-1.12;  $P < 0.0001$ ), and stroke of 13% (HR: 1.13; 95% CI: 1.02-1.25;  $P = 0.02$ ).<sup>13</sup> Several clinical trials are currently underway to determine the effectiveness of Inclisiran in reducing cardiovascular risk (Table 1).

Bempedoic acid, an inhibitor of the enzyme adenosine triphosphate-citrate lyase, determines the suppression of cholesterol synthesis by stimulating the upregulation of LDLR on hepatocytes with a consequent increase in the blood clearance of LDL-C. This molecule has been shown to be effective in reducing LDL-C in the CLEAR Harmony trial; in particular, the intake of a fixed dose of bempedoic acid combined with ezetimibe was found

to be able to reduce the share of LDL-C significantly more than placebo (38.0%,  $P < 0.001$ ), ezetimibe alone (23.2%,  $P < 0.001$ ) or bempedoic acid alone (17.2%,  $P < 0.001$ ).<sup>14</sup> Being a drug with a different mechanism of action from statins and ezetimibe, bempedoic acid will be a further weapon available to clinicians, particularly useful especially in patients who do not reach the optimal LDL-C target despite maximal therapy or as a molecule alternative in all those subjects intolerant to statins.

Last but not least, the molecules that selectively act on the lipoprotein-lipase (LPL) system deserve to be mentioned: the LPL is an enzyme responsible for the hydrolysis of the triglycerides contained in the circulating lipoproteins and its action determines a decrease of plasma triglycerides. This enzyme is regulated with a negative feedback mechanism by ANGPTL4, ANGPTL3 and APOC3, which reduce its activity.<sup>15</sup> The identification of carriers of loss of function mutations of the ANGPTL4 gene and the discovery that these subjects, as well as individuals with gain of function mutations in the LPL gene, have a 35% lower plasma triglyceride concentration ( $P = 0.003$ ) and a 53% reduced risk ( $P = 0.04$ ) of coronary heart disease compared with controls led the scientific community to develop targeted therapies; currently, several antisense oligonucleotides silencing APOC3 or ANGPTL3 and a monoclonal antibody that selectively inhibits ANGPTL3 are being tested (Table 2).

## Final remarks

We strongly believe that the ever finer understanding of the pathophysiological mechanisms underlying dyslipidemias

**Table 1** Innovative therapeutic strategies and prevalent lipid fractions

Lipid fraction	Drug	Mechanism	RCT
LDL-C	Bempedoic acid Inclisiran	ATP citrate-lyase inhibitor Anti-RNA PCSK9	CLEAR-Harmony ORION-1,2,3,4 HPS/TIMI65
TG + LDL-C	Evinacumab IONIS-ANGPTL3-Rx Volanesorsen	ANGPTL3 antibody ANGPTL3 antisense oligonucleotide APOC3 antisense oligonucleotide	Yes Yes COMPASS/APPROACH
Lp(a)	Pelacarsen	RNA antisense oligonucleotide	HORIZON

**Table 2** Gene therapy in development and treatment of dyslipidemias

Journal	Author	Drug	Target	Outcome
N Engl J Med, 2015	Gaudet D <i>et al.</i>	Antisense Oligonucleotide vs. mRNA (ISIS 304801), ISIS Pharma	APOC3	TG levels
N Engl J Med, 2017 N Engl J Med, 2020	Dewey FE <i>et al.</i>	Human Monoclonal Antibody-Evinacumab, Regeneron Pharma	ANGPTL3	TG levels LDL-C levels ATS disease
N Engl J Med, 2017	Graham MJ <i>et al.</i>	Antisense Oligonucleotide vs. mRNA, Ionis Pharma	ANGPTL3	TG levels LDL-C levels ATS disease Hepatic TG Insulin sensitivity

through the novelties obtained through DNA genotyping will allow, in the short term, to select the optimal starting drug or combinations of drugs for each category of patients, in order to reduce cumulative exposure and bypass the current 'step up' approach which does not consider the vast individual variability present in dyslipidemic subjects.

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